

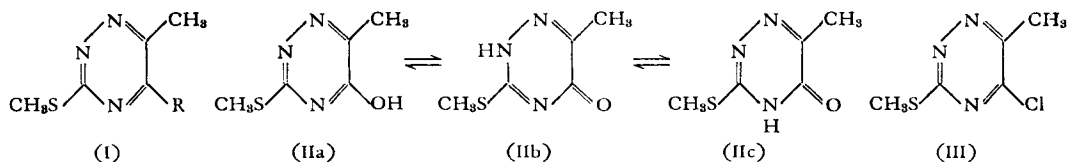
# 1,2,4-三嗪类化合物的研究

## II. 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪的不正常甲苯磺酰化反应\*

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为研究1,2,4-三嗪类化合物对肿瘤细胞作用的关系,拟合成5-取代-3-甲硫基-6-甲基-1,2,4-三嗪(I)类化合物。这类化合物通常系由相应的氯代衍生物经亲核性取代反应制备<sup>[1]</sup>,因此拟由3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)与氯化试剂作用以得到5-氯衍生物(III)作为合成的中间体,但未获得成功。3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)在三乙胺存在下与三氯化磷作用,经冰水分解,只得不能结晶的树脂状物质;改用五氯化磷和三氯化磷为氯化试剂或使用三氯化磷并添无水氯仿为稀释剂回馏作



用,亦均得树脂状物质或回收原作用物。

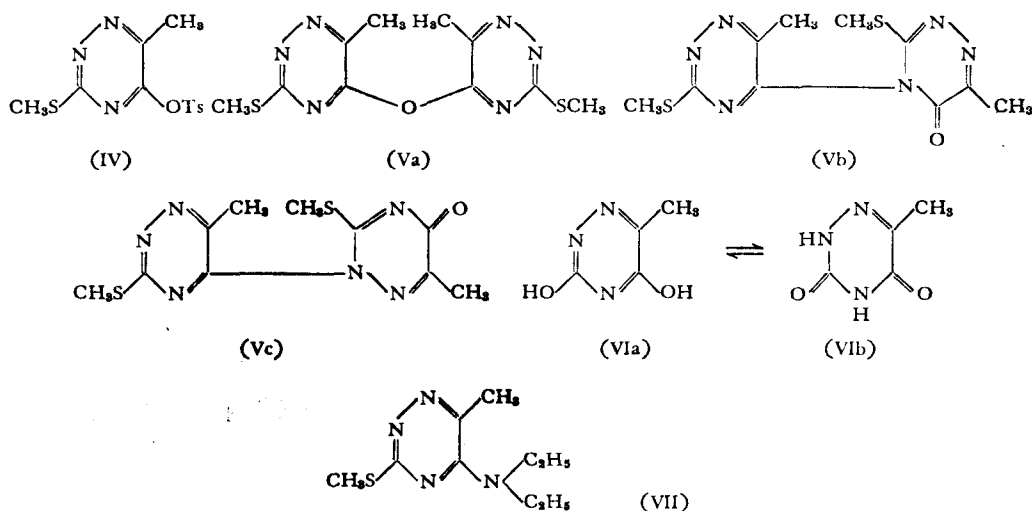
3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)在碱性条件下可能以烯醇式(IIa)存在,而其5-位碳原子的正电性较强,因此有可能利用甲苯磺酰化反应经相应的对甲苯磺酸酯(IV)以制备5-氯衍生物(III)。3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)与无水吡啶在10°和对甲苯磺酰氯作用,于生成的固体物中加水则全部溶解,经放置析出熔点为154—155°的淡黄色鳞片状晶体,可溶于乙醇、苯等有机溶剂中,但不溶于水。经元素分析及分子量测定,得经验式为 $C_{10}H_{12}N_6OS_2$ (V),收率85%。化合物V用10%氯代乙酸或1N盐酸回馏水解,则分别得81%及46.5%的3,5-二羟基-6-甲基-1,2,4-三嗪(VI);用1N氢氧化钠水解得48%的3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)。根据这些反应,化合物V应为二分子的3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)的脱水产物,其结构可能为(Va), (Vb)或(Vc)。

化合物V与二乙胺于室温或回馏温度作用均得熔点为124—126°的含硫化合物。根据元素分析,是3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪(VII),而不可能是3-甲硫基

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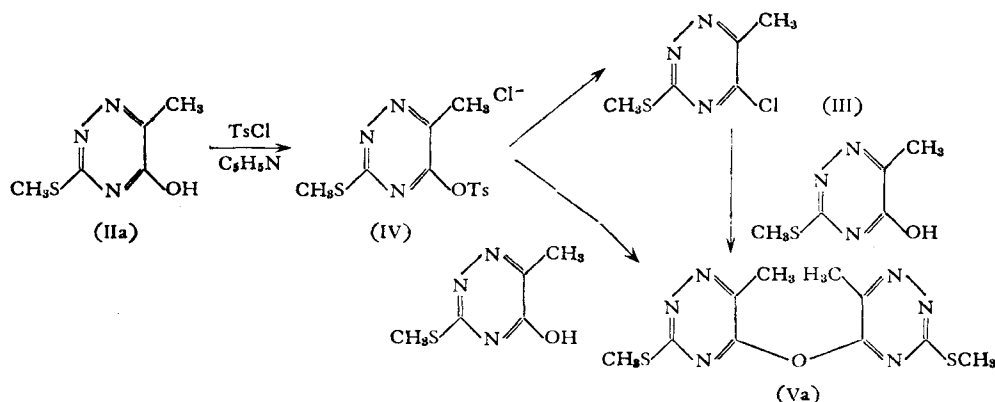
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被胺解的产物。这化合物在 1N 盐酸或 10% 碳酸钠溶液中加热水解均得高熔点物质。此外化合物 V 在乙醇溶液中与一系列的脂肪胺或芳香胺均易进行胺解反应, 得到相应的 5-取代氨基衍生物, 并且这些 5-取代氨基衍生物亦不能再进一步与二乙胺产生胺解反应, 有关的工作将另文发表。

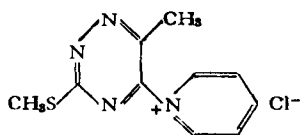
化合物 V 的可能结构中, Va 为醚衍生物, Vb 为酰胺衍生物, Vc 为胺衍生物。根据化合物 V 易于产生一系列的胺解及水解反应, 其性质和醚类化合物相近; 而 Vb 的酰胺基或 Vc 的胺基在乙醇中与脂肪胺或芳香胺进行胺基取代的前例则不多。因此化合物 V 的结构以 Va 的可能性较大。

初步设想化合物 Va 的生成可能经下列途径或经其他中间体过程:

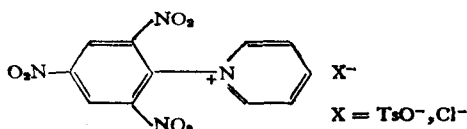


根据这种假设, 在反应过程中先生成的固体物可能为活性很强的中间体。因此将 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (II) 在无水吡啶中与对甲苯磺酰氯作用, 生成的固体物过滤, 相继用无水吡啶及无水氯仿洗涤, 干燥后得到熔点为 138—140° (分解) 的黄色粉末, 此化合物溶于水, 其水溶液与硝酸银溶液立即生成氯化银沉淀; 根据元素分析, 其经验式为  $C_{10}H_{11}N_4S$  (VIII), 收率 81%。化合物 VIII 在水中回流水解得到 80% 的 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (II)。根据化合物 VIII 的水溶度, 水溶液显氯离子反应, 说

明是盐；它可以水解为 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪和吡啶的性质和 2,4,6-三硝基苯酚在吡啶中和对甲苯磺酰氯作用生成鏽盐 (IX)<sup>[2]</sup> 的性质一致，因此化合物 VIII 的结构为氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鏽盐。

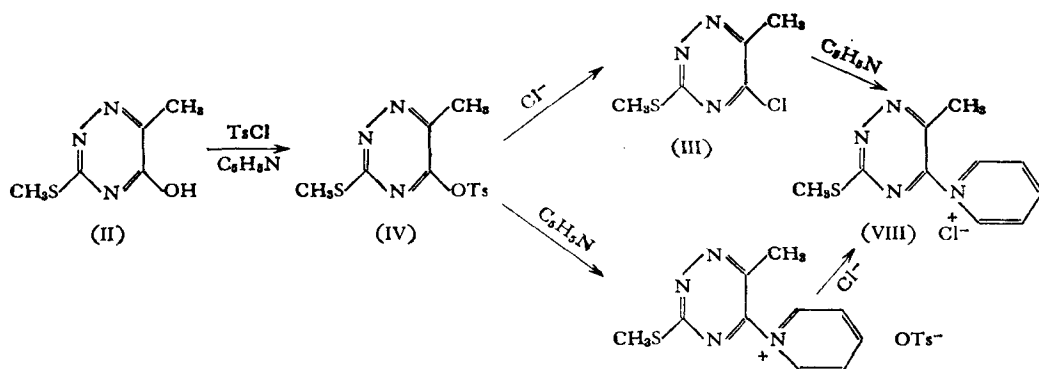


(VIII)

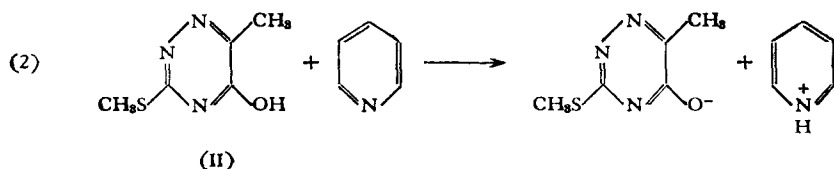
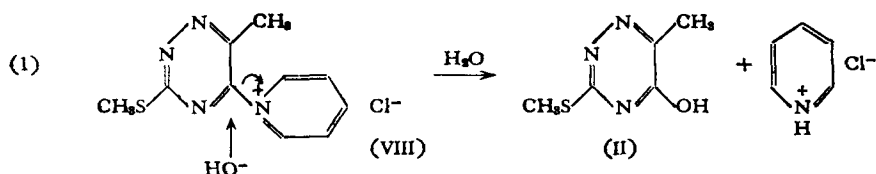


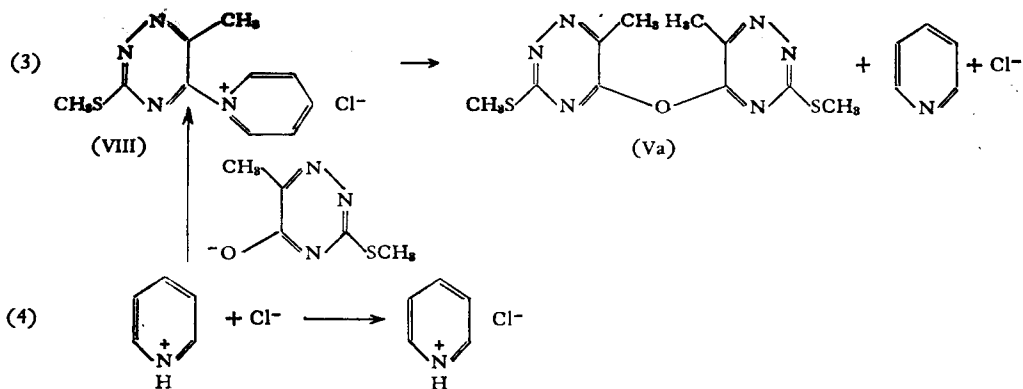
(IX)

我們认为中间体氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鏽盐 (VIII) 的生成，可能系經活性很强的 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪对甲苯磺酸酯 (IV) 或 3-甲硫基-5-氯-6-甲基-1,2,4-三嗪 (III)：

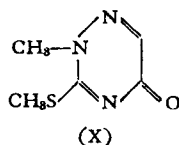


鏽盐 VIII 在水中加热則水解为 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (II)；但在有微量吡啶存在下，或用直接析离的未經洗滌精制的粗产品与水回馏，均得到化合物 Va。由此可肯定化合物 Va 的生成系通过吡啶鏽盐 (VIII)，其生成历程可能系由于鏽盐 (VIII) 先水解为 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (II)，后者再于鏽盐 (VIII) 的 5-位进行置换反应的结果。反应中加入的吡啶則作为质子受体，使水解生成的 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪形成负离子，以增速置换反应，不致使与之竞争的水解反应得占优势。





此外,尚进行有关化合物V的紅外吸收光谱的分析。化合物V在1666 厘米<sup>-1</sup>及1250 厘米<sup>-1</sup>处有强吸收峰(图1)。Horák 等<sup>[3]</sup>进行3,5-二巯基-2,3,4,5-四氫-1,2,4-三嗪类化合物及2-甲基-3-甲硫基-5-羰基-2,5-二氫-1,2,4-三嗪(X)在二氧六环中的紅外吸收光谱的工作,认为前者的C=O吸收峰在1664—1734 厘米<sup>-1</sup>,后者的C=O吸收峰在



1674 厘米<sup>-1</sup>。根据上述数据,化合物V既具C=O(1666 厘米<sup>-1</sup>)也具C—O—C(1250 厘米<sup>-1</sup>)结构,这似不可能。为确证这类化合物5-位C=O基在固态时紅外吸收峰的位置,我們作一些这类型化合物在固态时紅外吸收光谱,其C=O吸收峰的位置为:

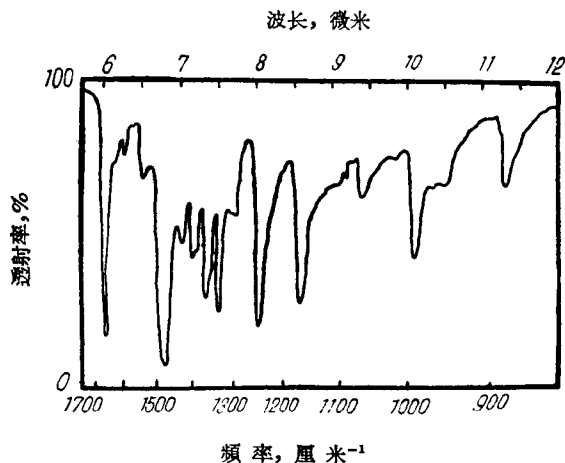
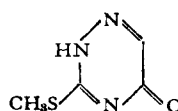
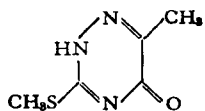


图1 化合物V的紅外吸收光谱

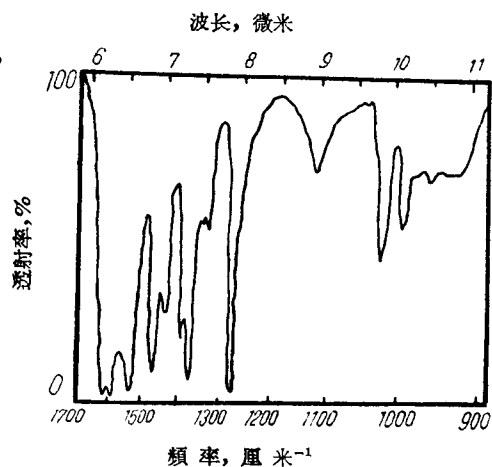
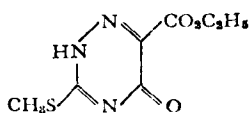
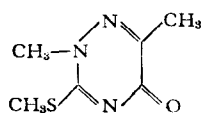
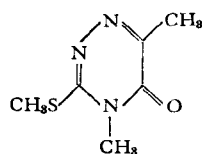


图2 3-甲硫基-5-巯基-6-甲基-2,5-二氫-1,2,4-三嗪(II)的紅外吸收光谱

(XII) 1640 厘米<sup>-1</sup>(XIII) 1639 厘米<sup>-1</sup>(XIV) 1668 厘米<sup>-1</sup>

这些化合物的  $C_5=O$  吸收峰在光谱中均为最强,且强度很大。2,6-二甲基-3-甲硫基-5-羰基-2,5-二氢-1,2,4-三嗪(XIII)的  $C_5=O$  吸收峰在 1639 厘米<sup>-1</sup>, 4,6-二甲基-3-甲硫基-5-羰基-4,5-二氢-1,2,4-三嗪(XIV)的  $C_5=O$  吸收峰在 1668 厘米<sup>-1</sup>, 在化合物 IIb, XI 及 XII 的  $C=O$  吸收峰在 1626—1640 厘米<sup>-1</sup> 间, 因此 IIb, XI, XII 和 XIII 一样拟为类对醌式结构, XIV 为类邻醌式结构。

根据以上红外吸收光谱的分析,化合物 V 在 1666 厘米<sup>-1</sup> 处的吸收峰可能系由类邻醌式结构的  $C_5=O$  基所致, 因而排除 Va 及 Vc 结构的可能。但是根据化合物 V 可进行一系列的胺解反应、水解反应、以及 5-取代氨基-3-甲硫基-6-甲基-1,2,4-三嗪类化合物不能再与二乙胺进行胺解反应<sup>[4]</sup> 的事实, 说明其结构应为 Va。因为化合物 Va 在 1666 厘米<sup>-1</sup> 的吸收峰强度不如化合物 IIb, XI—XIV 的  $C_5=O$  基吸收峰的强度大, 并且按照 Davison 等<sup>[5]</sup> 对缩胺脲类红外吸收光谱的分析认为在 1665 厘米<sup>-1</sup> 附近的吸收峰是由  $C=N$  所引起, 其强度(最大为 7)可以  $C=O$  吸收峰的强度(最大为 9)相近, 所以我们认为化合物 Va 在 1666 厘米<sup>-1</sup> 的吸收峰可能为  $C=N$  结构的伸展频率。由于对 1,2,4-三嗪类化合物红外吸收光谱的研究不够完全, 尚不能完全肯定化合物 V 在 1666 厘米<sup>-1</sup> 吸收峰的来源, 故也不能完全排除它为 Vb 的可能, 但以 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(Va)的可能性较大, 有关的工作尚待进行。

3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II) 在无水吡啶中与对甲苯磺酰氯作用生成相应的吡啶鎓盐(VIII)或醚类化合物(Va), 均可进一步得到相应的 5-取代衍生物。由这类反应的条件、收率以及产物的活性, 有可能成为置换杂环化合物中羟基的有利反应, 有关的工作正在进行。

## 实 验 部 分\*

### (一) 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II)的氯化反应

1. 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪<sup>[6]</sup> 1 克, 加入新蒸馏的三氯氧化磷 10 毫升及三乙胺 2 毫升, 在油浴上回馏两小时, 溶液由无色变为深棕色。将作用物倾入冰水中分解, 得到棕色树脂状物质, 此棕色物质用一般方法处理均不能得纯品。

2. 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 1 克, 加入新蒸馏的三氯氧化磷 10 毫升, 五氯化磷 1 克及无水氯仿 5 毫升, 在油浴上回馏一小时。反应后减压蒸去氯仿及三氯氧化磷, 然后倾入冰水中分解, 得棕色树脂状物质, 此树脂状物质用一般方法处理均未得纯品。

\* 本文中熔点均未校正。元素分析为本系分析室曹竹兰、李颖同志所作; 红外吸收光谱为中国医学科学院药物研究所及北京化工研究院代作, 作者谨致谢意。

3. 1 克 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪与 1 毫升新蒸馏的三氯化磷及无水氯仿 10 毫升混合。将混合物在 40° 加热一小时, 冷却后有淡黄色晶体析出。过滤, 用无水氯仿洗涤仍得原来的 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪。

## (二) O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(Va)

于 1 克 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (6.37 毫克分子) 中加入 4 毫升经氢氧化钾处理的无水吡啶, 再加入 1.6 克对甲苯磺酰氯 (8.39 毫克分子), 搅拌均匀。此时对甲苯磺酰氯溶解成淡黄色溶液而 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪不溶。以上混合物在密闭情况下于 10° 放置并时时振荡。五、六小时以后反应物成淡黄色糊状并随时间加长颜色逐渐加深。一昼夜后在反应物中加入 10 毫升水搅拌, 则反应物全部溶解。再于室温放置三、四小时后有黄棕色鳞片状晶体析出。过滤, 用少量水洗涤, 自 50% 乙醇重结晶得淡黄色鳞片状晶体的 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 0.8 克, 熔点 154—155°, 收率 85.1%。

分析:  $C_{10}H_{12}N_6OS_2$

计算值%: C, 40.54; H, 4.05; N, 28.38

实验值%: C, 40.58; H, 4.10; N, 28.39

分子量(Rast 法):

计算值: 296

实验值: 291

红外吸收光谱(溴化钾片): 3448—3279(弱), 1666(强), 1600(弱), 1538(弱), 1475(最强), 1429(中), 1403(中), 1366(强), 1337(强), 1250(强), 1174(强), 1070(弱), 993(中), 889(弱), 774 厘米<sup>-1</sup>(弱)。

## (三) O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(Va)的水解反应

1. 0.5 克 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪与 10 毫升 10% 一氯乙酸回流四小时, 反应液减压蒸干, 残渣用乙醚洗涤, 用水重结晶, 得 3,5-二羟基-6-甲基-1,2,4-三嗪(VI) 0.35 克, 熔点 210—211°, 与已知样品<sup>[6]</sup>的混合熔点不降低, 收率 81%。

2. 0.4 克 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪, 加 10 毫升 1N 盐酸, 回流一小时, 反应液减压蒸干, 残渣用水重结晶, 得 3,5-二羟基-6-甲基-1,2,4-三嗪(VI) 0.2 克, 熔点 210—211°, 与已知样品<sup>[6]</sup>的混合熔点不降低, 收率 46.5%。

3. 0.2 克 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪, 加 5 毫升 1N 氢氧化钠, 回流三小时。反应液减压蒸干, 用盐酸中和到酸性, 滤出沉淀, 用水重结晶得 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II) 0.1 克, 收率 48%, 熔点 225—227°, 与已知样品<sup>[6]</sup>的混合熔点不降低。

红外吸收光谱(溴化钾片): 2703—2597(中), 1626(最强), 1600(最强), 1538(最强), 1471(强), 1443(中), 1399(中), 1370(最强), 1282(最强), 1124(最弱), 1026(弱), 990

(弱), 790(中), 767厘米<sup>-1</sup>(最弱)。

#### (四) O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(Va)的胺解反应

于0.2克 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪中加入新蒸二乙胺 10 毫升。在 20° 放置并不时振摇, 反应物渐成黄色溶液, 三小时后固体全部消失, 继续放置一夜, 析出黄色结晶。自乙醇-乙醚-石油醚重结晶, 得 0.1 克 3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪(VII), 熔点 124—126°, 收率 71.4%。样品钠熔后呈阳性硫离子反应。

分析: C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>S

计算值%: C, 50.94; H, 7.55; N, 26.41

实验值%: C, 50.71; H, 7.93; N, 26.01

#### (五) 3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪(VII)的水解反应

1. 40 毫克 3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪加 1 毫升 1N 盐酸, 回馏三小时, 减压蒸干得白色粉末 15 毫克, 不溶于水及一般有机溶剂, 为高熔点物质。

2. 于 0.2 克 3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪加 5 毫升 10% 碳酸钠溶液, 反应物成淡黄色溶液。在石棉网上回馏二小时, 减压蒸干, 得黄色固体, 加入盐酸使呈酸性, 过滤, 用水洗涤得 0.1 克淡黄色粉末, 不溶于水及一般有机溶剂; 为高熔点物质。

#### (六) 氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐(VIII)

于 1 克 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(6.37 毫克分子)中加 4 毫升经氢氧化钾处理的无水吡啶, 然后加入 1.6 克对甲苯磺酰氯(8.39 毫克分子)搅拌均匀。在密闭情况下于 10° 放置廿四小时, 时时搅拌, 有固体生成。过滤, 用 20 毫升无水吡啶洗涤, 继用 15 毫升无水氯仿洗去吡啶。产物于真空干燥得到黄色粉末状的氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐 1.3 克。热至 135° 变黑, 138—140° 分解, 收率 81%。

分析: C<sub>10</sub>H<sub>11</sub>ClN<sub>4</sub>S

计算值%: C, 47.11; H, 4.32; N, 22.00; Cl, 13.95

实验值%: C, 47.10; H, 4.32; N, 21.90; Cl, 13.18

#### (七) 氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐(VIII)的水解反应

于 0.5 克氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐中加蒸馏水 10 毫升使全部溶解为黄色溶液, 回馏一小时, 有吡啶臭味产生。冷却后析出黄色针状结晶的 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(II) 0.25 克, 熔点 225—227°, 与已知样品<sup>[6]</sup>的混合熔点不降低, 收率 80%。

#### (八) 氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐(VIII)在吡啶水溶液中的反应

0.5 克氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐中加蒸馏水 10 毫升及吡啶 5 滴, 反应物在石棉网上加热十分钟, 有晶体析出, 继续加热半小时。冷却后过滤, 得黄色鳞片状的 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪(Va) 0.25 克, 熔点 154—155°, 与已知样品的混合熔点不降低。收率几乎定量。

## 摘 要

3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (II) 在无水吡啶中与对甲苯磺酰氯作用, 得氯化 N-[5-(3-甲硫基-6-甲基)-1,2,4-三嗪基]-吡啶鎓盐 (VIII)。它在含微量吡啶的水溶液中回馏得结构可能是 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (Va) 的化合物。此化合物与二乙胺作用得 3-甲硫基-5-二乙氨基-6-甲基-1,2,4-三嗪 (VII), 后者水解得高熔点的物质。O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (Va) 的结构是借其水解反应及胺解反应等加以推论。对于这类化合物的红外吸收光谱也进行讨论。作者对于 3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪在吡啶中与对甲苯磺酰氯作用生成 O-[5'-(3'-甲硫基-6'-甲基)-1',2',4'-三嗪基]-3-甲硫基-5-羟基-6-甲基-1,2,4-三嗪 (Va) 的反应历程提出建议。

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## CHEMISTRY OF 1,2,4-TRIAZINES

## II. AN ANOMALOUS TOSYLATION OF 3-METHYLMERCAPTO-5-HYDROXY-6-METHYL-1,2,4-TRIAZINE

LI CHUN, CHANG LI-HO, TUNG CHEN-HUAN,

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(Department of Pharmacy, Peking Medical College)

## ABSTRACT

3-Methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) reacted with *p*-toluenesulfonyl chloride in anhydrous pyridine to give N-[5-(3-methylmercapto-6-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII), the latter compound gave O-[5'-(3'-methylmercapto-6'-methyl)-1',2',4'-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) on refluxing with water containing small amount of pyridine. The structure of O-[5'-(3'-methylmercapto-6'-methyl)-1',2',4'-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) was elucidated by its hydrolysis to 3,5-dihydroxy-6-methyl-1,2,4-triazine (VI) with aqueous chloroacetic acid or hydrochloric acid and to 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) with aqueous sodium hydroxide. Ammonolysis of O-[5'-(3'-methylmercapto-6'-methyl)-1',2',4'-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) with diethylamine gave 3-methylmercapto-5-diethylamino-6-methyl-1,2,4-triazine (VII) which formed high melting-point substances on hydrolysis with aqueous solution of hydrochloric acid or sodium carbonate. The infrared spectra of some 1,2,4-triazine derivatives were studied.



## CHEMISTRY OF 1,2,4-TRIAZINES

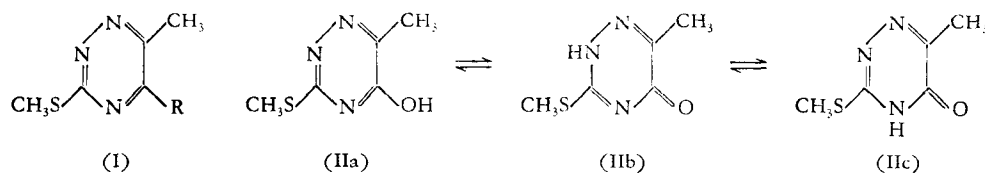
II. AN ANOMALOUS TOSYLATION REACTION OF  
3-METHYLMERCAPTO-5-HYDROXY-  
6-METHYL-1, 2, 4-TRIAZINE\*

LI CHUN (李 钧), CHANG LI-HO (张礼和), TUNG CHEN-HUAN (董振环)\*\*,

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Synthesis of 5-substituted-3-methylmercapto-6-methyl-1,2,4-triazines (I) was attempted in order to study their physiological activities against tumour cells. These kinds of compounds were usually prepared<sup>[1]</sup> from the corresponding hydroxy compounds through the chloro-derivatives by nucleophilic substitution. Attempts to chlorinate 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II, 3-methylmercapto-5-oxo-6-methyl-2,5-dihydro-1,2,4-triazine, 3-methylmercapto-5-oxo-6-methyl-4,5-dihydro-1,2,4-triazine) with phosphorus chloride under various conditions were unsuccessful.



Since 3-methylmercapto-5-oxo-6-methyl-dihydro-1,2,4-triazine (IIb, IIc) can be tautomerized in basic medium as an enol (3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine, IIa) and the carbon atom at 5-position is more positive, therefore, the 5-hydroxyl group may be tosylated to its *p*-toluenesulphonic ester (III), and the 5-chloro derivative (IV) may be obtained through its *p*-toluenesulphonic ester by exchange.

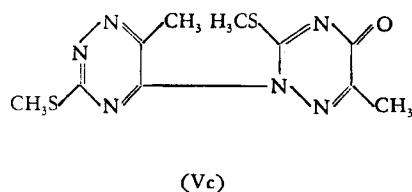
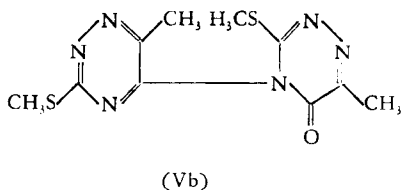
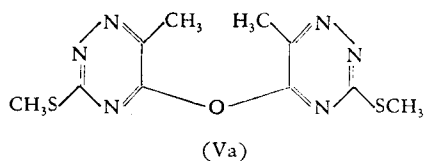


When 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) was reacted with *p*-toluenesulphonyl chloride in anhydrous pyridine at 10°, a yellow paste was obtained after

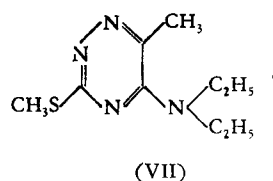
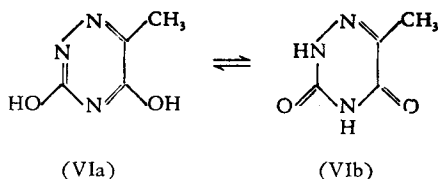
\* First published in Chinese in *Acta Chimica Sinica*, Vol. 29, No. 5, pp. 336—343, 1963.

\*\* Present address, Hopei Medical College.

standing in a refrigerator for six hours. Then water was added, and yellow prisms were deposited from the yellow solution on standing or warming. The yellow prisms after recrystallization from 50% aqueous ethanol melted at 154–155°, and were soluble in ethanol and benzene, but insoluble in water. Elementary analysis and molecular weight determination indicated that empirical formula for such prisms was  $C_{10}H_{12}N_6OS_2$  (V), the yield being 85% of the theory. Hydrolysis of compound V with 10% monochloroacetic acid or 1 N hydrochloric acid gave 3,5-dihydroxy-6-methyl-1,2,4-triazine (VI, 3,5-dioxo-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazine) in 81.5% and 46.5% yield respectively; with 1 N sodium hydroxide it gave 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) in 48% yield. From the hydrolytic products isolated, compound V can be derived from two molecules of 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) with elimination of one molecule of water, and the following possible structures (Va, Vb, and Vc) were proposed:

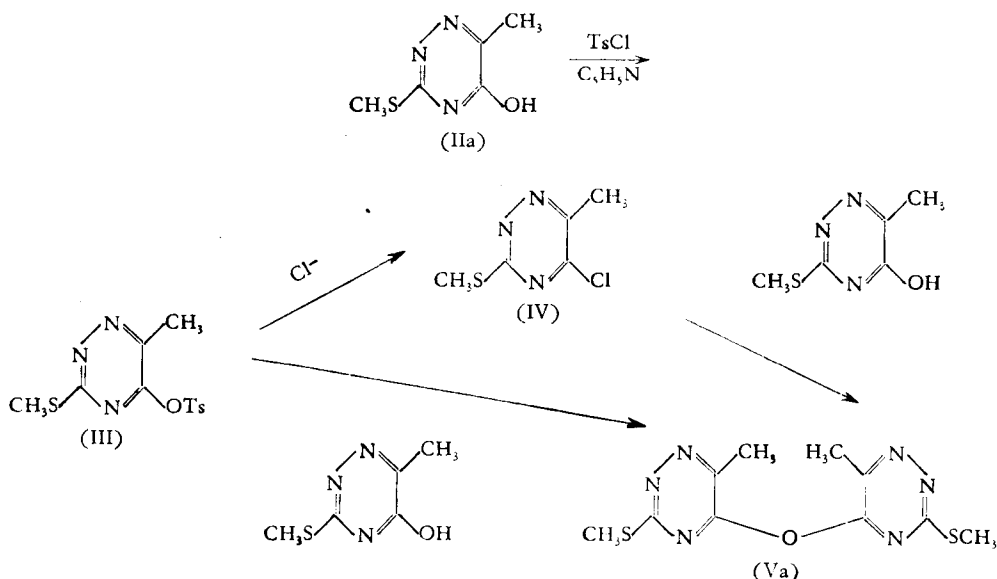


Reaction of compound V with diethylamine in ethanol either at room temperature or after being heated under reflux gave a compound  $C_9H_{16}N_4S$ , melting at 124–126°. According to its elementary analysis and the presence of sulphur in the molecule, ammonolysis could not take place at the 3-methylmercapto group. Therefore this compound should be 3-methylmercapto-5-diethylamino-6-methyl-1,2,4-triazine (VII). When it was used

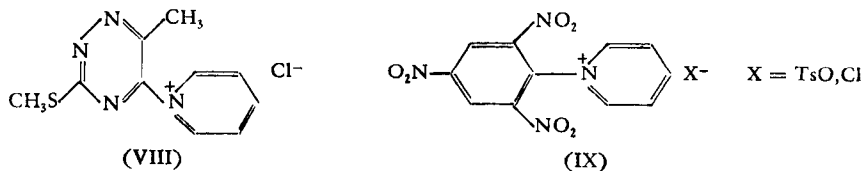


to hydrolyse with 1 N hydrochloric acid or 10% sodium carbonate solution, only polymerized powder of high melting point was obtained. Furthermore, when compound V reacted with a series of aliphatic and aromatic amines in ethanol, there were obtained 5-substituted amino-3-methylmercapto-6-methyl-1,2,4-triazines, which could not be substituted with diethylamine<sup>[2]</sup>. Accordingly, the structure of an ether, Va, was more probable for compound V.

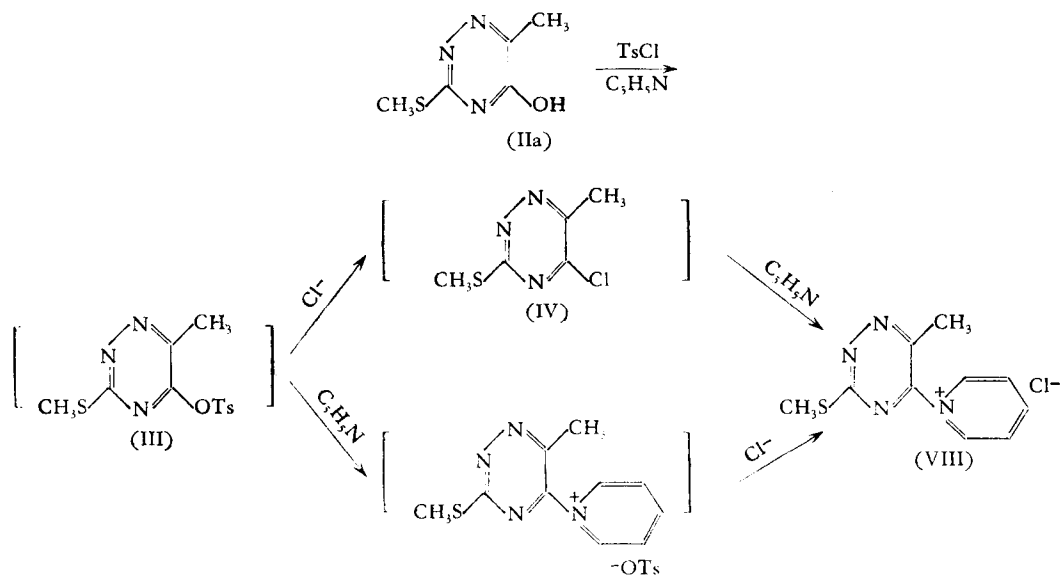
We may assume that compound Va is formed through the following routes or other intermediates:



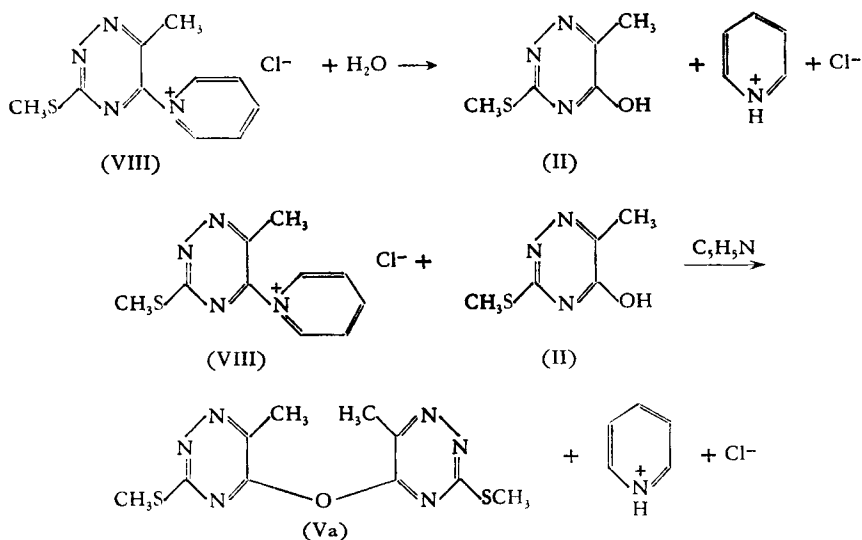
The solid material first formed might be the active intermediate. When 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) was reacted with *p*-toluenesulphonyl chloride in pyridine, isolated by filtration, and washed successively with anhydrous pyridine and anhydrous chloroform, yellow powder was obtained with empirical formula  $\text{C}_{10}\text{H}_{11}\text{N}_4\text{SCl}$  (VIII) melted at  $138-140^\circ$  with decomposition. It was freely soluble in water, and the aqueous solution deposited silver chloride immediately on adding silver nitrate. The yield of compound VIII was 81% of the theory. Refluxed with water, compound VIII gave 80% of 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II), and a strong smell of pyridine could be detected. From the facts that compound VIII was soluble in water freely, and that aqueous solution showed positive test for chloride ion and could be hydrolysed to 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine and pyridine, it may be seen that it was analogous to the pyridinium salt (IX)<sup>[3]</sup> formed from 2,4,6-trinitrophenol and *p*-toluenesulphonyl chloride in pyridine. Therefore, the structure N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride was assigned to compound VIII.



We may further assume that N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII) might be formed through the intermediate 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine *p*-toluenesulphonic ester (III) or through 3-methylmercapto-5-chloro-6-methyl-1,2,4-triazine (IV) as follows:



During the hydrolysis of N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII), when trace of pyridine was added or the aqueous solution of the crude compound VIII was heated under reflux, compound Va was isolated as the sole product in nearly quantitative yield. Accordingly, the following mechanism was proposed:



N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII) was first hydrolysed to 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II), which, then, attacked N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride in the presence of pyridine at the 5-position nucleophilically.

In the present work, the infrared absorption spectrum of compound V was also studied. This compound showed absorption bands at  $1666\text{ cm}^{-1}$  and  $1250\text{ cm}^{-1}$  in potassium bromide disc (Fig. 1). According to Horák<sup>[4]</sup> 3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazines

and 2-methyl-3-methylmercapto-5-oxo-2,5-dihydro-1,2,4-triazine (X) showed absorption bands characteristic for carbonyl group in dioxane at  $1664\text{--}1734\text{ cm}^{-1}$  and  $1674\text{ cm}^{-1}$  respectively. Therefore, compound V should possess both  $\text{C}=\text{O}$  ( $1666\text{ cm}^{-1}$ ) and  $\text{C}-\text{O}-\text{C}$  ( $1250\text{ cm}^{-1}$ ) functions in the molecule, but this seems impossible. In order to elucidate the absorption band characteristic for carbonyl group of triazine derivatives at the 5-position in the solid state, the infrared absorption spectra of some of 1,2,4-triazine derivatives were studied. The locations of the  $\text{C}_5=\text{O}$  groupings were:

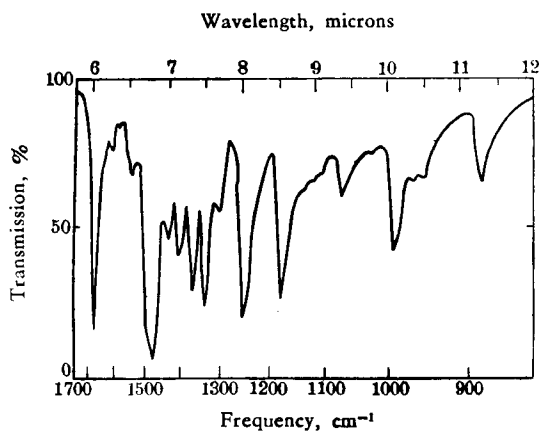
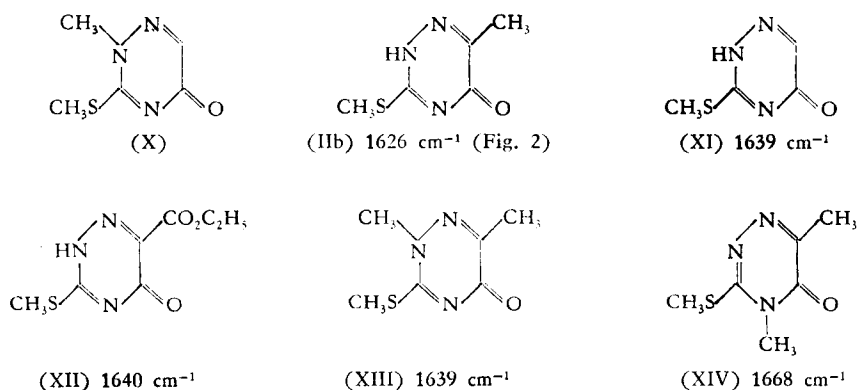


Fig. 1. Infrared absorption spectrum of compound V.

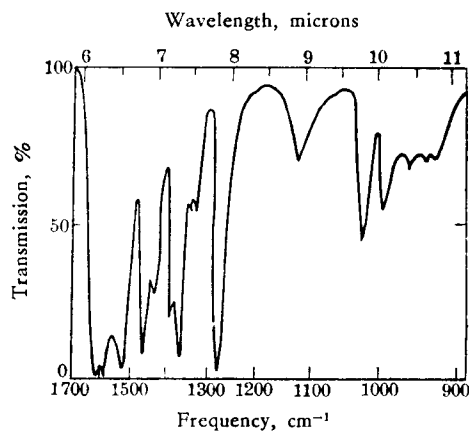


Fig. 2. Infrared absorption spectrum of 3-methylmercapto-5-oxo-6-methyl-2,5-dihydro-1,2,4-triazine (IIb).

Of these compounds, the absorption bands characteristic for  $\text{C}_5=\text{O}$  were the strongest and with a very high intensity. It was found that the absorption band for  $\text{C}_5=\text{O}$  group of 2,6-dimethyl-3-methylmercapto-5-oxo-2,5-dihydro-1,2,4-triazine (XIII) was located at  $1639\text{ cm}^{-1}$ , that of 4,6-dimethyl-3-methylmercapto-5-oxo-4,5-dihydro-1,2,4-triazine (XIV) was at  $1668\text{ cm}^{-1}$ , and the characteristic carbonyl group absorption bands of compound II, XI and XII were found at  $1626\text{--}1640\text{ cm}^{-1}$ . It could, therefore, be concluded that compounds II, XI and XII were analogous to XIII as quasi-*p*-quinoid structure, while XIV as quasi-*o*-quinoid structure.

From the discussion of the spectroscopic data cited above, the absorption band at  $1666\text{ cm}^{-1}$  for compound V may be due to the presence of  $\text{C}_5=\text{O}$  group in a quasi-*o*-quinoid structure, and thus the possible structures of Va and Vc are eliminated. However, from the chemical evidences that compound V could be ammonolysed with a series of aliphatic and aromatic amines, and hydrolysed with acids and alkalis, and that 5-substituted amino-3-methylmercapto-6-methyl-1,2,4-triazines could not be substituted with diethylamine, it may be seen that structure Va was more probable. The absorption band at  $1666\text{ cm}^{-1}$  of compound Va might be interpreted as follows. Firstly, it could be seen from the spectrum that the absorption band at  $1666\text{ cm}^{-1}$  of compound Va was weaker than that characteristic for  $\text{C}_5=\text{O}$  functions of compounds IIb, XI—XIV. Secondly, according to the studies about the infrared absorption spectra of semicarbazones by Davison<sup>[5]</sup> the band in the neighbourhood of  $1665\text{ cm}^{-1}$  was attributable to  $\text{C}=\text{N}$  bond, and the intensity was comparable with that of  $\text{C}=\text{O}$  function (maximum 9 if the maximum  $\text{C}=\text{N}$  function is 7). Therefore, the absorption band at  $1666\text{ cm}^{-1}$  of compound Va might be attributed to the  $\text{C}=\text{N}$  stretching vibration. It must be mentioned here that the knowledge about the infrared absorption spectra of 1,2,4-triazine derivatives is far from being complete, and the interpretation of the band at  $1666\text{ cm}^{-1}$  of compound V is not yet conclusive. Therefore, the possible structure Vb could not be definitely eliminated. However, O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) was more probable. Further investigations are in progress.

The N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII) and O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) might be further converted into 5-substituted-3-methylmercapto-6-methyl-1,2,4-triazines (I) as mentioned above. From the ease of formation and the high yield and activity of these compounds, new routes for substitution of the hydroxyl group in heterocyclic compounds may be developed. This work is in progress in our laboratory.

#### EXPERIMENTAL\*

##### 1. O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va)

In a glass-stoppered bottle was placed 1.6 g (8.39 millimoles) of *p*-toluenesulphonyl chloride dissolving in 4 ml anhydrous pyridine previously dried over fused potassium hydroxide, then 1 g of 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II, 6.37 millimoles) was added with vigorous shaking to form a yellow paste or sometimes a yellow viscous solution. The mixture was kept in a refrigerator for six hours to complete the reaction. To the yellow paste, 10 ml of water was added and a clear yellow solution resulted. The solution was let to stand at room temperature or warmed for 3—4 hours till light yellow prisms were deposited. The crystals were filtered, washed with water, and then recrystallised from 50% aqueous ethanol to give 0.8 g of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1, 2, 4-triazine

\* All melting points given were uncorrected. Microlyses were carried out by Misses Tsao Chu-lan and Li Ying, infrared absorption spectra by Institute of Materia Medica, Chinese Medical Science, Peking and by Institute of Chemical Engineering, Peking, to whom the authors express their grateful thanks.

(Va) in 85.1% yield of the theory, m.p. 154—155°. It was soluble in ethanol or benzene, but insoluble in water.

Analysis:  $C_{10}H_{12}N_6S_2O$

Calculated %: C, 40.54; H, 4.05; N, 28.38.

Found %: C, 40.58; H, 4.10; N, 28.39.

Molecular weight (micro Rast Camphor Method)

Calculated: 296.

Found: 291.

Main infrared absorption bands (KBr disc, Fig. 1): 3448—3279 (w), 1666 (s), 1600 (w), 1538 (w), 1475 (vs), 1429 (m), 1403 (m), 1366 (s), 1337 (s), 1250 (s), 1174 (s), 1070 (w), 993 (m), 889 (w), 774  $cm^{-1}$  (w).

2. *Hydrolysis of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va)*

(1) One half of a gramme of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1, 2, 4-triazine (Va) was refluxed with 10 ml of 10% monochloroacetic acid over a wire gauze for four hours, and the solution was evaporated with the aid of a water pump to dryness. The residue was washed with ether and recrystallised from water to give 0.35 g of 3,5-dihydroxy-6-methyl-1,2,4-triazine (VI), 81% yield of the theory, melting at 210—211°, the melting point was not depressed on admixture with an authentic sample<sup>[6]</sup>.

(2) Four tenths of a gramme of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) and 10 ml of 1 N hydrochloric acid were heated under reflux for one hour. The solution was evaporated to dryness with a water pump, and the residue was washed with ether, and recrystallised from water to give 0.2 g (46.5% yield) of 3,5-dihydroxy-6-methyl-1,2,4-triazine (VI), m.p. 210—211°, mixed melting point with an authentic sample<sup>[6]</sup> was also 210—211°.

(3) One fifth of a gramme of O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1, 2, 4-triazine (Va) was hydrolysed with 5 ml of 1 N sodium hydroxide for three hours. The reaction mixture was evaporated to dryness under reduced pressure, and then acidified with hydrochloric acid to get slightly acidic. The residue was filtered and recrystallised from hot water to give 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) in 48% yield (0.1 g), m.p. 225—227°; mixed melting point with an authentic sample<sup>[6]</sup> was not depressed.

Main infrared absorption bands of 3-methylmercapto-5-oxo-6-methyl-2,5-dihydro-1,2,4-triazine (IIb, KBr disc, Fig. 2): 2703—2597 (m), 1626 (vs), 1600 (vs), 1538 (vs), 1471 (s), 1443 (m), 1399 (m), 1370 (vs), 1282 (vs), 1124 (vw), 1026 (w), 990 (w), 790 (m), 767  $cm^{-1}$  (vw).

3. *Ammonolysis of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va)*

One fifth of a gramme of O-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1, 2, 4-triazine (Va) and 10 ml of freshly distilled diethylamine were kept at room temperature (20°) with occasional shaking. The colour of the reaction mixture turned yellow and the solid material dissolved completely after

three hours. After standing overnight, the deposited crystals were collected and recrystallised from ethanol-ether-petroleum ether mixture to give 3-methylmercapto-5-diethylamino-6-methyl-1,2,4-triazine (VII), melted at 124–126°. The yield was 71.4% of the theory (0.1 g). A sample of the product showed positive test for sulphide ion after sodium fusion.

Analysis:  $C_9H_{16}N_4S$

Calculated %: C, 50.94; H, 7.55; N, 26.41.

Found %: C, 50.71; H, 7.93; N, 26.01.

4. *Attempted hydrolysis of 3-methylmercapto-5-diethylamino-6-methyl-1, 2, 4-triazine (VII)*

(1) 3-methylmercapto-5-diethylamino-6-methyl-1,2,4-triazine (VII, 40 mg) was refluxed with 1 ml of 1 N hydrochloric acid for three hours. The solution after evaporation to dryness gave a white polymerized powder of high melting point, which was insoluble in water and most organic solvents.

(2) 10% sodium carbonate solution (5 ml) was added to 0.2 g of 3-methylmercapto-5-diethylamino-6-methyl-1, 2, 4-triazine (VII), and the yellow solution was heated over a wire gauze under reflux for two hours. The mixture was evaporated to dryness, then hydrochloric acid was added to the yellow residue to assure its slight acidity. The solid material collected was washed with water, and then a light yellow powder was obtained, m.p. >360°. This material was insoluble in water and most organic solvents.

5. *N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII)*

One and six tenths of a gramme of *p*-toluenesulphonyl chloride (8.39 milimoles) were dissolved in 4 ml of anhydrous pyridine in a glass-stoppered bottle, and then one gramme of 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II, 6.37 milimoles) was added with vigorous shaking. The yellow paste obtained after standing in a refrigerator was filtered, washed with anhydrous pyridine ( $2 \times 10$  ml) and anhydrous chloroform ( $2 \times 10$  ml), and dried in a vacuum desiccator. The N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII) obtained as yellow powder weighed 1.3 g (81% yield); it darkened at 135° and melted at 138–140° with decomposition. This compound (VIII) was freely soluble in water and showed positive test for chloride ion with silver nitrate immediately.

Analysis:  $C_{10}H_{11}N_4SCl$

Calculated %: C, 47.11; H, 4.32; N, 22.00; Cl, 13.95.

Found %: C, 47.10; H, 4.32; N, 21.90; Cl, 13.18.

6. *Hydrolysis of N-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-pyridinium chloride (VIII)*

One half of a gramme of N-[5'-(3'-methylmercapto-6'-methyl)-1, 2, 4-triazinyl]-pyridinium chloride (VIII) was dissolved in 10 ml of water to form a clear solution, and the solution was heated under reflux for one hour. A strong smell of pyridine could be detected. After cooling, yellow needles of 3-methylmercapto-5-hydroxy-6-methyl-1, 2, 4-triazine (II) were collected. It weighed 0.25 g (80% yield of the theory), m.p. 225–227°, showing no depression in melting point on admixture with an authentic sample<sup>[6]</sup>.



7. *Reaction of N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII) in aqueous solution containing pyridine*

N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII, 0.5 g) was dissolved in 10 ml of water and five drops of pyridine were added. The solution was heated under reflux. After 10 minutes yellow prisms were found to deposit and heating was continued for further half an hour. The yellow prisms were filtered when the solution was cold. It weighed 0.25 g; the yield was nearly quantitative. It melted at 154–155°; mixed melting point with a sample of O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) as previously described was not depressed.

#### SUMMARY

3-Methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) reacted with *p*-toluenesulphonyl chloride in anhydrous pyridine to give N-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-pyridinium chloride (VIII). The latter compound gave O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) on refluxing with water containing small amount of pyridine. The structure of O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) was elucidated by its hydrolysis to 3,5-dihydroxy-6-methyl-1,2,4-triazine (VI) with aqueous monochloroacetic acid or hydrochloric acid and to 3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (II) with aqueous sodium hydroxide. Ammonolysis of O-[5'-(3'-methylmercapto-6'-methyl)-1,2,4-triazinyl]-3-methylmercapto-5-hydroxy-6-methyl-1,2,4-triazine (Va) with diethylamine gave 3-methylmercapto-5-diethylamino-6-methyl-1,2,4-triazine (VII) which formed a polymerized substance of high melting point on hydrolysis with aqueous solution of hydrochloric acid or sodium carbonate. The infrared absorption spectra of some 1,2,4-triazine derivatives were studied.

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