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# Syntheses of s-Triazolo [4,3-*a*] Pyrimidine Derivatives

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7-Substituted-s-triazolo[1,5-*a*]pyrimidines were synthesized by the condensation of 3-amino-1,2,4-triazole (ATA) with ethyl acetoacetate and their biological activities were described.[1] The present paper deals with the condensation of 5-substituted-ATA-derivatives, for example, 3-amino-5-hydroxy-1,2,4-triazole (I) and 3-amino-5-mercapto-1,2,4-triazole (II), with ethyl acetoacetate, acetylacetone and ethyl cyanoacetate.

By the condensation of ATA with $\beta$-chlorocrotonic acid ester, Birr *et al.*[2] prepared 7-hydroxy-derivatives containing the ring system of (IV). There is, however, no report as to 3-hydroxy-derivatives. On the other hand, the compound (VII) prepared from (II) and acetylacetone by the authors was identical with that synthetized by Bower *et al.*[3] and Williams[7] with 2-pyrimidylhydrazine and excess carbon disulfide.

The compounds obtained are shown in Fig. 1 and Table I. These compounds contained a ring system related to purines, to 2-($\alpha$-hydroxybenzyl)-benzimidazole which has antiviral activity,[4] to imidazolo-pyridine which is herbicidal,[5] and are expected to exhibit some biological activities. Some of them showed herbicidal or fungicidal activity, on which have been reported elsewhere.[1]

## EXPERIMENTAL

*5, 7-Dimethyl-3-mercapto-s-triazolo [4,3-a] pyrimidine, (VII).* The starting compounds, (I) and (II), were prepared according to the method of Godfrey *et al.*[6]

A mixture of 1.9 g of II[6] and 2.5 g of acetylacetone in 15 ml of acetic acid was refluxed for about 5 hr. During the reaction the solution turned yellow-brown. After completion of the reaction, the acetic acid was removed *in vacuo* on a steam bath. The resulting precipitate was collected, washed with ether, and recrystallized from ethanol to obtain 2.6 g of pale yellow needles, mp 243～244°C.

Williams prepared this compound by the condensation of 2-hydrazino-4,6-dimethylpyrimidine with carbon disulfide in pyridine.[7] Mp and analytical data are identical with our preparation.

$C_7H_8N_4S$: Calcd. C, 46.66% H, 4.48% N, 31.10%
Found C, 46.80 H, 4.62 N, 31.05

*4-Amino-7-hydroxy-3-mercapto-s-triazolo [4,3-a] pyrimidine, (V).* 1.5 g of ethyl cyanoacetate and 1.2 g of II were added to a solution of sodium ethoxide which was prepared from 0.25 g of Na and 15 ml of abs. ethanol. The mixture was refluxed for 9 hr. During the reaction the mixture turned dark yellow.

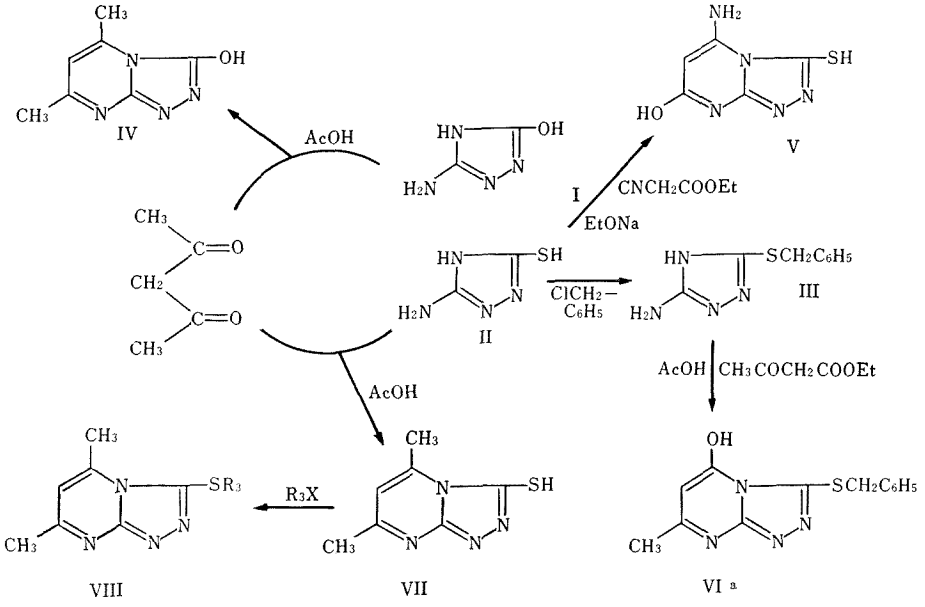
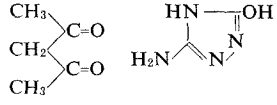
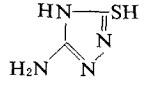
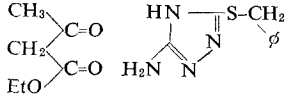
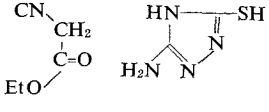
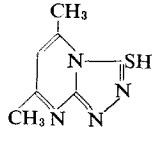



FIG. 1. Synthesis of Triazolo[4,3-*a*]pyrimidine Derivatives.

TABLE I. SYNTHESES OF TRIAZOLO[4,3-*a*]PYRIMIDINE DERIVATIVES

| Reaction partner | Reaction: Temp. (°C) | Reaction: Time (hr) | Reaction: Solvent | $R_1$ | $R_2$ | $R_3$ | Yield (%) | Mp (°C) | Molecular formula | Formula | Refr. |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 110 | 5 | AcOH | $CH_3$ | $CH_3$ | OH | 65 | 256~7 | $C_7H_8ON_4$ | IV | |
|  | 100 | 5 | AcOH | $CH_3$ | $CH_3$ | SH | 72 | 243~4 | $C_7H_8N_4S$ | VII | 3, 7, 8 |
|  | 110 | 6 | AcOH | OH | $CH_3$ | $SCH_2C_6H_5$ | 78 | 247 | $C_{13}H_{12}ON_4S$ | VI a | |
| | | | | | | $SCH_2C_6H_5Cl$ | 60 | 242 | $C_{13}H_{11}ON_4SCl$ | VI b | |
| | | | | | | $SCH_2C_6H_5NO_2$ | 69 | 263 | $C_{13}H_{11}O_3N_5S$ | VI c | |
|  | 70 | 9 | EtOH containing EtONa | $NH_2$ | OH | SH | 60 | 300> | $C_5H_5ON_5S$ | V | |
|  I-$CH_3$ | 25 | 2.5 | 1 N NaOH | $CH_3$ | $CH_3$ | $SCH_3$ | 89 | 152~3 | $C_8H_{10}N_4S$ | VIII a | 7 |
| Cl-$CH_2$-$\phi$ | 70~80 | 2.5 | 〃 | $CH_3$ | $CH_3$ | $SCH_2C_6H_5$ | 66 | 133.5~4.5 | $C_{14}H_{14}N_4S$ | b | |
| Cl-$CH_2$-COOH | 90~95 | 4.5 | | $CH_3$ | $CH_3$ | $SCH_2COOH$ | 85 | 179.5 | $C_9H_{10}O_2N_4S$ | c | 3 |
| Cl-$CH_2$-$CH_2$-COOH | 100 | 2 | $H_2O$ | $CH_3$ | $CH_3$ | $S(CH_2)_2COOH$ | 83 | 212 | $C_{10}H_{12}O_2N_4S$ | d | |
| Cl-$CH_2$-$CH_2$-OH | 25 | 24 | 1 N NaOH | $CH_3$ | $CH_3$ | S-$CH_2$-$CH_2OH$ | 69 | 113 | $C_9H_{12}ON_4S.H_2O$ | e | |
| Cl-$CH_2C_6H_4Cl$ | 60~80 | 2.5 | 〃 | $CH_3$ | $CH_3$ | $SCH_2C_6H_4Cl$ | 91 | 143~5 | $C_{14}H_{14}N_4SCl$ | f | |

After cooling, the precipitated sodium salts were collected, dissolved in water and treated with charcoal. The filtrate was acidified with conc.HCl, and the resulting precipitate was recrystallized from ethanol to obtain colorless needles, mp above 300°C (decomp.). Yield, 0.7 g.

$C_5H_5ON_5S$ : Calcd. C, 32.79% H, 2.75% N, 38.25%
Found C, 32.98 H, 2.78 N, 38.02

*3-Benzylthio-5-hydroxy-7-methyl-s-triazolo[4,3-a]pyrimidine, (VI a).* A mixture of 1 g of 3-amino-5-benzylthio-1,2,4-triazole (III), which was prepared from II and benzyl chloride, and 1 g of ethyl acetoacetate in 12 ml of acetic acid was refluxed on an oil bath for 6 hr. During the reaction colorless crystals appeared. The acetic acid was removed *in vacuo* and the residue recrystallized from ethanol and water to afford 1.2 g of colorless prisms, mp 247°C.

$C_{13}H_{12}ON_4S$: Calcd. C, 57.35% H, 4.44% N, 20.58%
Found C, 57.33 H, 4.55 N, 20.31

*3-(p-Chloro)benzylthio-5-hydroxy-7-methyl-s-triazolo-[4,3-a]pyrimidine, (VI b).* A suspension of 3-amino-5-(*p*-chloro)benzylthio-1,2,4-triazole (4.5 g) in acetic acid(30 ml) containing ethyl acetoacetate (2.6 g) was heated under reflux for 6 hr. After chilling, the product was collected and recrystallized from aq. ethanol as colorless needles, mp 242°C. Yield, 4.8 g.

$C_{13}H_{11}ON_4SCl$ :
Calcd. C, 50.91% H, 3.61% N, 18.27%
Found C, 50.88 H, 3.73 N, 18.18

*3-(p-Nitro)benzylthio-5-hydroxy-7-methyl-s-triazolo [4,3-a]pyrimidine, (VI c).* According to the same procedure just mentioned, pale yellow needles of the VI c was obtained from 3-amino-5-(*p*-nitro)benzylthio-1,2,4-triazole (1.7 g) and ethyl acetoacetae (0.9 g). Mp 263°C, yield 2 g.

$C_{13}H_{11}O_3N_5S$ :
Calcd. C, 49.21% H, 3.49% N, 22.08%
Found C, 49.52 H, 3.51 N, 21.94

*5, 7-Dimethyl-3-hydroxy-s-triazolo[4,3-a]pyrimidine, (IV).* A mixture of 0.3 g of I and 0.45 g of acetylacetone in 3 ml of acetic acid was refluxed for about 5 hr on an oil bath. During the reaction the solution turned yellow, and yellow crystals appeared. The acetic acid was removed *in vacuo*. The resulting residue was recrystallized from methanol to afford 0.4 g of yellow needles, mp 257°C.

$C_7H_8ON_4$ :
Calcd. C, 51.21% H, 4.91% N, 34.13%
Found C, 51.24 H, 4.98 N, 34.16

*S-Alkylation of 5,7-dimethyl-3-mercapto-s-triazolo[4,3-a]pyrimidine, (VIII a~f).* These compounds (VIII a~f) were obtained with a fairly good yield, by treating VII with alkyl halides under the conditions given in the Table I. The recrystallization was carried out from aq.methanol (VIII e), aq.ethanol (VIII d), ethanol (VIII b, f), benzene-ethanol (VIII c) and benzene (VIII a) respectively. In all cases the derivatives were colorless needles.

(VIII a)
$C_8H_{10}N_4S$ Calcd. C 49.48% H, 5.19% N, 28.85%
Found C 49.78 H, 5.45 N, 28.85

(VIII b)
$C_{14}H_{14}N_4S$ Calcd. C 62.21 H, 5.22 N, 20.73
Found C 62.50 H, 5.38 N, 20.68

(VIII c)
$C_9H_{10}O_2N_4S$ Calcd. C 45.38 H, 4.23 N, 23.52
Found C 45.37 H, 4.31 N, 23.70

(VIII d)
$C_{10}H_{12}O_2N_4S$ Calcd. C 47.62 H, 4.80 N, 22.22
Found C 47.51 H, 4.88 N, 22.17

(VIII e)
$C_9H_{12}ON_4S.H_2O$ Calcd. C 44.62 H, 5.83 N, 23.13
Found C 44.18 H, 6.02 N, 22.82

(VIII f)
$C_{14}H_{14}N_4SCl$ Calcd. C 55.11 H, 4.58 N, 18.41
Found C 55.43 H, 4.42 N, 18.39

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