

REACTION OF 3-AMINOPYRAZOLE-4-CARBOXAMIDES WITH ETHYL 3-ETHOXY-  
METHYLENE-2,4-DIOXOVALERATE. SYNTHESIS OF 6-ACETYL-7-CARBETHOXY-  
PYRAZOLO[1,5-a]PYRIMIDINE-3-CARBOXAMIDE

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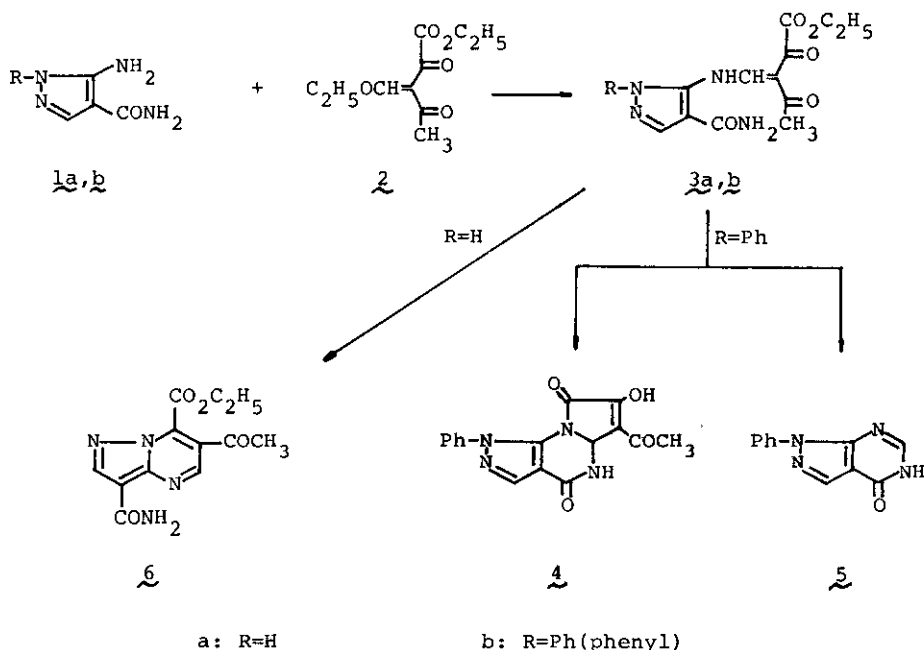
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Abstract — Reaction of ethyl 3-ethoxymethylene-2,4-dioxovalerate (2) with the 3-aminopyrazole-4-carboxamides (1a,b) gave the corresponding aminomethylene derivatives (3a,b), which are cyclized to the pyrazolo[1,5-a]pyrimidine (6) and pyrrolo[1,2-a]pyrazolo[3,4-e]pyrimidine-1,5-dione (4), respectively. Some reactions of 6 are also described.

We<sup>1</sup> have previously reported the reaction of o-aminobenzamide derivatives with ethyl 3-ethoxymethylene-2,4-dioxovalerate (2) to give pyrrolo[1,2-a]quinazoline-1,5-diones, having the interesting biological activity.<sup>2</sup> It seems of much interest to examine the utility of 2 to synthesize other heterocyclic compounds. In the present paper, we report that the 3-aminopyrazole-4-carboxamides (1a,b) react with 2 to afford pyrrolo[1,2-a]pyrazolo[3,4-e]pyrimidine (4) and the pyrazolo[1,5-a]pyrimidine (6), respectively.

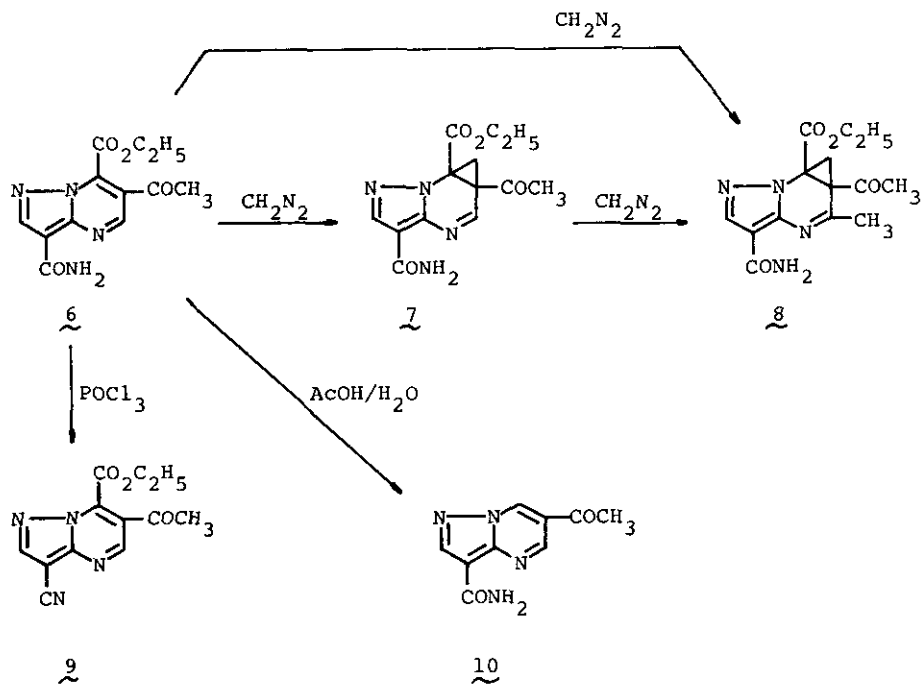
Ethyl 3-ethoxymethylene-2,4-dioxovalerate (2) reacts readily with 1a,b in ethanol under cooling to give 85-90% yield of the ethyl 3-aminomethylene-2,4-dioxovalerates (3a,b) [mp 146-147° (3a)<sup>3</sup> and mp 174-175° (3b)]. Refluxing 3b in acetic acid containing a catalytic amount of trifluoroacetic acid for 3 hr furnished a separate mixture of 3-acetyl-3a,4-dihydro-2-hydroxy-8-phenylpyrrolo[1,2-a]pyrazolo[3,4-e]pyrimidine (5), mp 301-302° (lit.<sup>4</sup> 299°), in yield of 48% and 46%, respectively. The structure of 4 was determined by its elemental analysis and the following spectral data:  $\nu_{\max}$  (KBr) 3340, 1740, 1640;  $\lambda_{\max}$  (EtOH) 229 (4.34), 261 (sh) (4.23), 334 (3.96);  $\delta$  (DMSO-d<sub>6</sub>) 2.40 (2H, s, COCH<sub>3</sub>), 6.25 (1H, s, CH), 7.80 (1H, s, NH), 8.05 (1H, s, C<sub>6</sub>-H), 10.20 (1H, bs, OH). Compound 4 is soluble in NaHCO<sub>3</sub> solution and showed wine-red color when treated with FeCl<sub>3</sub>. These results are

closely similar to those previously reported.<sup>1</sup>



On the other hand, 3a was refluxed in ethanol for 5 minutes to furnish 6-acetyl-7-carbethoxypyrazolo[1,5-a]pyrimidine-3-carboxamide (6), mp 202-204°, in a quantitative yield, whose structural assignment was based on its elemental analysis and the spectral data :  $\nu_{\max}$  (KBr) 3400, 1760, 1695, 1660 ;  $\lambda_{\max}$  (EtOH) 257 (4.40), 312 (3.90) ;  $\delta$  (DMSO- $d_6$ ) 1.40 (3H, t,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 2.76 (3H, s,  $\text{COCH}_3$ ), 4.56 (2H, q,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 7.50 and 7.70 (each 1H, each bs,  $\text{NH}_2$ ), 8.83 (1H, s,  $\text{C}_2\text{-H}$ ), 9.50 (1H, s,  $\text{C}_5\text{-H}$ ) ; mass  $m/e$  276 ( $\text{M}^+$ ), 260 ( $\text{M}^+ - \text{NH}_2$ ). While the syntheses of some derivatives of pyrazolo[1,5-a]pyrimidine have hitherto been reported by many researchers<sup>5</sup>, there is no report on the synthesis of pyrazolo[1,5-a]pyrimidine possessing three carbonyl groups on ring. Compound 6 was directly obtained by condensation of 1a with 2 in boiling ethanol, without isolation of 3a, in 92% yield. Next, the reactivity of 6 was elucidated. It reacted smoothly with large excess of diazomethane in ether at room temperature (27-30°) leading to 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-5-methyl-6H-cyclopropa[5a,6a]pyrazolo[1,5-a]pyrimidine (8), mp 176-177°, in 98% yield. When the reaction of 6 with diazomethane was carried out under ice cooling, the isolated product was compound 7 (89% yield), mp 148-150°, which was subsequently methylated by action of diazomethane at room

temperature to 8.



The spectral data of these products are as follows : 7 mass  $m/e$  290 ( $M^+$ ) ;  $\nu_{\text{max}}$  (KBr) 3450, 1730, 1710, 1650 ;  $\delta$  (DMSO- $d_6$ ) 1.15 (3H, t,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 1.55 and 2.65 (each 1H, each d,  $J$  6 Hz,  $\text{CH}_2$ ), 2.53 (3H, s,  $\text{COCH}_3$ ), 4.15 (2H, q,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 7.20 and 7.40 (each 1H, each bs,  $\text{NH}_2$ ), 7.93 (1H, s,  $\text{C}_2\text{-H}$ ), 8.90 (1H, s,  $\text{C}_5\text{-H}$ ). 8 mass  $m/e$  304 ( $M^+$ ) ;  $\nu_{\text{max}}$  (KBr) 3400, 1740, 1700, 1660 ;  $\lambda_{\text{max}}$  (EtOH) 284 (3.95) ;  $\delta$  (DMSO- $d_6$ ) 1.15 (3H, t,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 1.55 and 2.50 (each 1H, each d,  $J$  6 Hz,  $\text{CH}_2$ ), 2.40 and 2.50 (each 3H, each s,  $2 \times \text{CH}_3$ ), 4.25 (2H, q,  $J$  6 Hz,  $\text{CH}_2\text{CH}_3$ ), 7.45 (2H, bs,  $\text{NH}_2$ ), 8.00 (1H, s,  $\text{C}_2\text{-H}$ ).

The results so far described indicate that 6 has reactive double bond on pyrimidine ring, and it appears to be of interest. Treatment of 6 with phosphorous oxychloride gave the corresponding cyano derivative (9), mp 152-153°, in 70% yield.

It was found that 6 took hydrolysis and decarboxylation to give 6-acetylpyrazolo[1,5-a]pyrimidin-3-carboxamide (10), mp 289-290°, [ $\delta$  (DMSO- $d_6$ ) 2.60 (3H, s,  $\text{COCH}_3$ ), 7.50 (2H, bs,  $\text{NH}_2$ ), 8.76 (1H, s,  $\text{C}_2\text{-H}$ ), 9.15 (1H, d,  $J$  2 Hz,  $\text{C}_7\text{-H}$ ), 10.00 (1H, d,  $J$  2 Hz,  $\text{C}_5\text{-H}$ )] in refluxing dilute acetic acid.

Further studies on the reactivity of the compound 6 and its related compounds are in progress.

## REFERENCES

1. T. Kurihara and Y. Sakamoto, Heterocycles, in press.
2. S.C. Bell and G. Conklin, U.S. Patent 3,707,468 [C.A., 1973, 78, 72188a].
3. Compound 3a showed the following nmr data :  $\delta$  (DMSO- $d_6$ ) 1.10 (3H, t,  $J$  6 Hz,  $CH_2CH_3$ ), 2.25 (3H, s,  $COCH_3$ ), 4.15 (2H, q,  $J$  6 Hz,  $CH_2CH_3$ ), 7.80 (1H, d,  $J$  5 Hz, CH), 8.00 (1H, s, pyrazole ring-H), 10.60 (1H, d,  $J$  5 Hz, NH).
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5. Y. Makisumi, Chem. Pharm. Bull. (Tokyo), 1962, 10, 612 ; ibid., 1962, 10, 620 ; J. Delettre, R. Balley, and J-P Mornon, J. Heterocyclic Chem., 1978, 15, 185.

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