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

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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 (4) and pyrrolo[1,2-a]pyrazolo[3,4-e]pyrimidine-1,5-dione (5), respectively. Some reactions of 5 are also described.

We 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. 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 (5), 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) 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. 299°), in yield of 48% and 46%, respectively. The structure of 5 was determined by its elemental analysis and the following spectral data: v max (KBr) 3340, 1740, 1640; λ max (EtOH) 229 (4.34), 261 (sh) (4.23), 334 (3.96); δ (DMSO-d6) 2.40 (2H, s, COCH3), 6.25 (1H, s, CH), 7.80 (1H, s, NH), 8.05 (1H, s, C6-H), 10.20 (1H, bs, OH). Compound 4 is soluble in NaHCO3 solution and showed wine-red color when treated with FeCl3. These results are
closely similar to those previously reported. 1

On the other hand, La was refluxed in ethanol for 5 minutes to furnish 6-acetyl-7-carbethoxy[1,5-α]pyrazolo[1,5-α]pyrimidine-3-carboxamide (6), mp 202-204°, in a quantitative yield, whose structural assignment was based on its elemental analysis and the spectral data : \( \nu_{\text{max}} \) (KBr) 3400, 1760, 1695, 1660 ; \( \lambda_{\text{max}} \) (EtOH) 257 (4.40), 312 (3.90) ; \( \delta \) (DMSO-\( \text{d}_6 \)) 1.40 (3H, t, \( J \) 6 Hz, CH\(_2\)CH\(_3\)), 2.76 (3H, s, COCH\(_3\)), 4.56 (2H, q, \( J \) 6 Hz, CH\(_2\)CH\(_3\)), 7.50 and 7.70 (each 1H, each bs, NH\(_2\)), 8.83 (1H, s, C\(_5\)-H), 9.50 (1H, s, C\(_5\)-H) ; mass m/e 276 (M\(^+\)), 260 (M\(^+\)-NH\(_2\)). While the syntheses of some derivatives of pyrazolo[1,5-α]pyrimidine have hitherto been reported by many researchers, there is no report on the synthesis of pyrazolo[1,5-α]pyrimidine possessing three carbonyl groups on ring. Compound 6 was directly obtained by condensation of 3a with 2 in boiling ethanol, without isolation of 3a, in 92% yield.

Next, the reactivity of 1 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-α]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 2 (89% yield), mp 148-150°, which was subsequently methylated by action of diazomethane at room
The spectral data of these products are as follows:  

$\mathcal{Z}$  mass m/e 290 ($M^+$); $\nu_{\text{max}}$ (KBr) 3450, 1730, 1710, 1650; $\delta$ (DMSO-$d_6$) 1.15 (3H, t, $\delta$ 6 Hz, CH$_2$CH$_3$), 1.55 and 2.65 (each 1H, each d, $\delta$ 6 Hz, CH$_2$), 2.53 (3H, s, COCH$_3$), 4.15 (2H, q, $\delta$ 6 Hz, CH$_2$CH$_3$), 7.20 and 7.40 (each 1H, each bs, NH$_2$), 7.93 (1H, s, C$_2$-H), 8.90 (1H, s, C$_5$-H).  

$\mathcal{Z}$  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, $\delta$ 6 Hz, CH$_2$CH$_3$), 1.55 and 2.50 (each 1H, each d, $\delta$ 6 Hz, CH$_2$), 2.40 and 2.50 (each 3H, each s, 2 × CH$_3$), 4.25 (2H, q, $\delta$ 6 Hz, CH$_2$CH$_3$), 7.45 (2H, bs, NH$_2$), 8.00 (1H, s, C$_2$-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]pyrimidine-3-carboxamide (10), mp 289-290°, $\delta$ (DMSO-$d_6$) 2.60 (3H, s, COCH$_3$), 7.50 (2H, bs, NH$_2$), 8.76 (1H, s, C$_2$-H), 9.15 (1H, d, $\delta$ 2 Hz, C$_7$-H), 10.00 (1H, d, $\delta$ 2 Hz, C$_5$-H) in refluxing dilute acetic acid.

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

3. Compound 3a showed the following nmr data: δ (DMSO-d₆) 1.10 (3H, t, J 6 Hz, CH₂CH₃), 2.25 (3H, s, COCH₃), 4.15 (2H, q, J 6 Hz, CH₂CH₃), 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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