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

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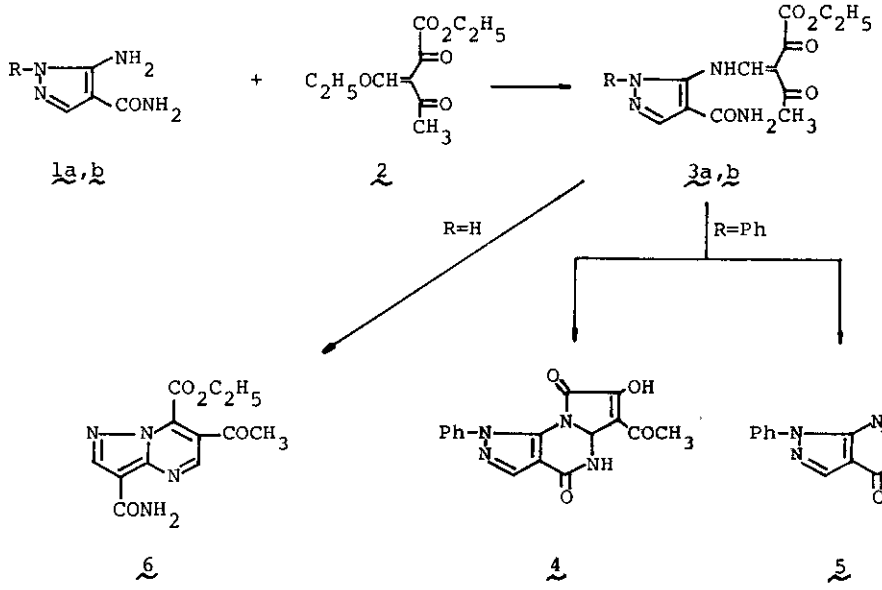
Abstract — Reaction of ethyl 3-ethoxymethylene-2,4-dioxovalerate (2) with the 3-aminopyrazole-4-carboxamides (1a,b) gave the corresponding aminomethylene derivatives (3a,b), which are cyclized to the pyrazolo[1,5-a]pyrimidine (6) and pyrrolo[1,2-a]-pyrazolo[3,4-e]pyrimidine-1,5-dione (4), respectively.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

We[1] 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.[2] 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)[3] 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.[4] 299°), in yield of 48% and 46%, respectively. The structure of 4 was determined by its elemental analysis and the following spectral data : ν_{max} (KBr) 3340, 1740, 1640 ; λ_{max} (EtOH) 229 (4.34), 261 (sh) (4.23), 334 (3.96) ; δ (DMSO-d_6) 2.40 (2H, s, $COCH_3$), 6.25 (1H, s, CH), 7.80 (1H, s, NH), 8.05 (1H, s, C_6-H), 10.20 (1H, bs, OH). Compound 4 is soluble in $NaHCO_3$ solution and showed wine-red color when treated with $FeCl_3$. These results are

closely similar to those previously reported.[1]



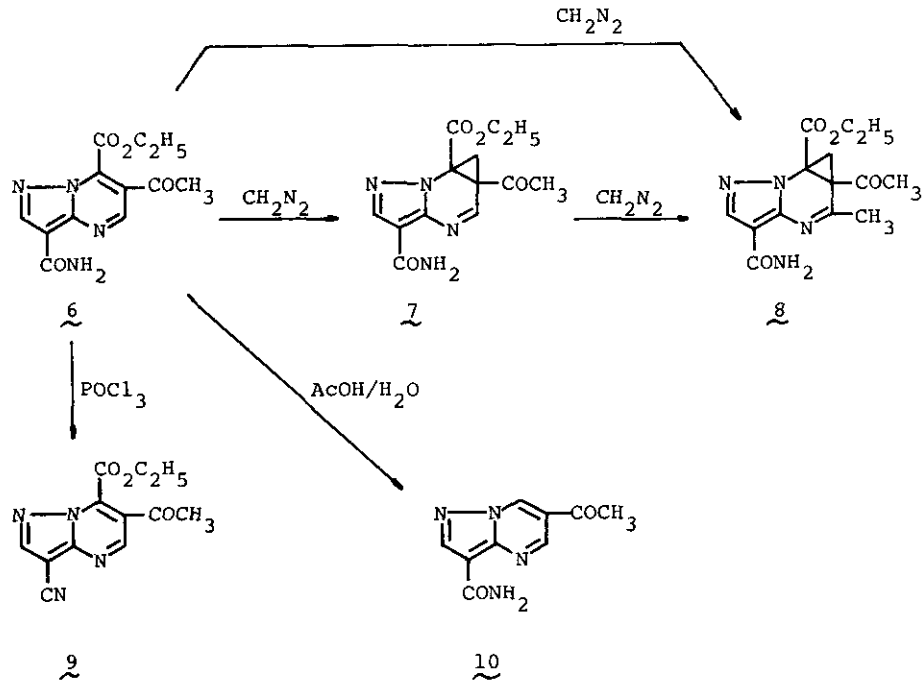
1a,b + 2 → 3a,b

3a,b: R=H → 6; R=Ph → 4 + 5

a: R=H b: R=Ph(phenyl)

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 : ν_{max} (KBr) 3400, 1760, 1695, 1660 ; λ_{max} (EtOH) 257 (4.40), 312 (3.90) ; δ (DMSO-d_6) 1.40 (3H, t, J 6 Hz, CH_2CH_3), 2.76 (3H, s, $COCH_3$), 4.56 (2H, q, J 6 Hz, CH_2CH_3), 7.50 and 7.70 (each 1H, each bs, NH_2), 8.83 (1H, s, C_2-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-a]pyrimidine have hitherto been reported by many researchers[5], 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^+) ; ν_{max} (KBr) 3450, 1730, 1710, 1650 ; δ (DMSO-d_6) 1.15 (3H, t, J 6 Hz, CH_2CH_3), 1.55 and 2.65 (each 1H, each d, J 6 Hz, CH_2), 2.53 (3H, s, $COCH_3$), 4.15 (2H, q, J 6 Hz, CH_2CH_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). 8 mass m/e 304 (M^+) ; ν_{max} (KBr) 3400, 1740, 1700, 1660 ; λ_{max} (EtOH) 284 (3.95) ; δ (DMSO-d_6) 1.15 (3H, t, J 6 Hz, CH_2CH_3), 1.55 and 2.50 (each 1H, each d, J 6 Hz, CH_2), 2.40 and 2.50 (each 3H, each s, 2 × CH_3), 4.25 (2H, q, J 6 Hz, CH_2CH_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°, [δ (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, J 2 Hz, C_7-H), 10.00 (1H, d, J 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.

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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 : δ (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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