A CONVENIENT SYNTHESIS OF [1,2]DIAZEPINONES BY THE REACTION OF HYDRAZINES ON 5-ACETYL PYRAN-2,6-DIONE AND 2-PYRONES

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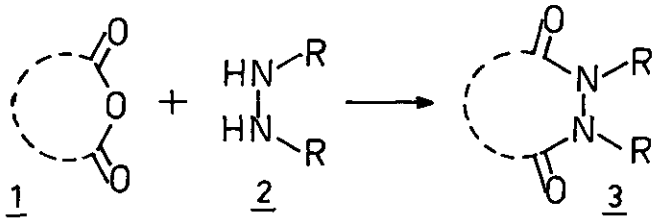
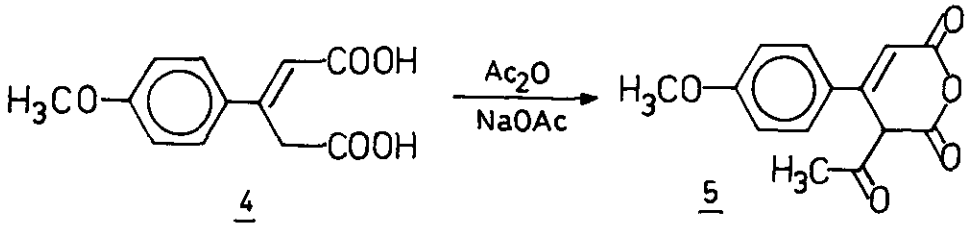
Abstract- Reactions of hydrazine and phenyl hydrazine with 5-acetylpyran--2,6-dione (5) yielded [1,2]diazepinones 8 and 12, respectively. The formation of 12 was via the acid carboxamide 10. The diazepinone 8 was also obtained from 2-pyrones 13 and 14 with hydrazine, while the latter also afforded pyrazolodiazepinone 15. Both 13 and 14 on treatment with phenylhydrazine furnished N-phenyldiazepinone 9.

Cyclic anhydrides (1) react with hydrazines (2) to form 3,ω-dioxo-1,2-diazaheterocycles (3) with a larger ring size. In light of this 5-acetyl-4-(4-methoxyphenyl)-5H-pyran-2,6-dione (5) was thought to provide an interesting anhydride framework with activated endocyclic double bond and



1 2 3

a reactive acetly group at the 5-position. Further, the facile ring cleavage and recyclization leading to 2-pyrone formation[1,2] indicated the possibility of the formation of [1,2]diazepin-3--one instead of the [1,2]diazepin-3,7-dione from 5. The compound 5 could be easily obtained from 3-(4-methoxyphenyl)-2-pentenedioic acid[3,4] (4) by the treatment with acetic anhydride and sodium acetate under Perkin reaction conditions.

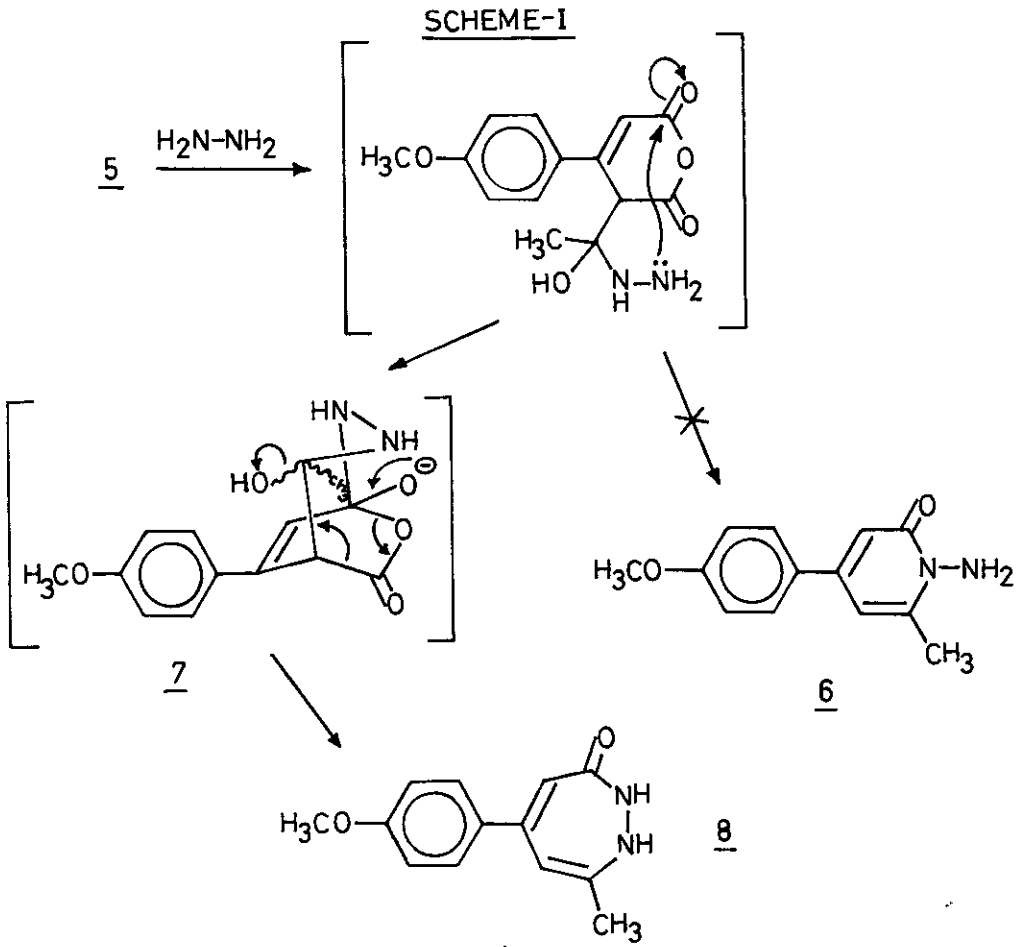


4 5

Hydrazine hydrate reacted spontaneously with 5 and afforded 1,2-dihydro-5-(4-methoxyphenyl)-

-7-methyl [1,2]diazepin-3-one (8). The other possible structure 6 was ruled out on the basis of spectral data and the inability of the product to form the benzylidine derivative[5] with benzaldehyde. The formation of 8 was initiated by the nucleophilic attack of hydrazine on stereochemically easily accessible acetyl carbonyl carbon which is expected to be more electrophilic than the other two carbonyl carbons in 5 to form the intermediate hydrazide. The $-NH_2$ group of this hydraziee, being more basic than -NH-, attacked internally on the anhydride carbonyl at 2--position leading to the opening of the anhydride ring followed by decarboxylation (Scheme-I). The facile decarboxylation even at room temperature led us to believe that the formation of 8 takes place through a plausible intermediate (7).

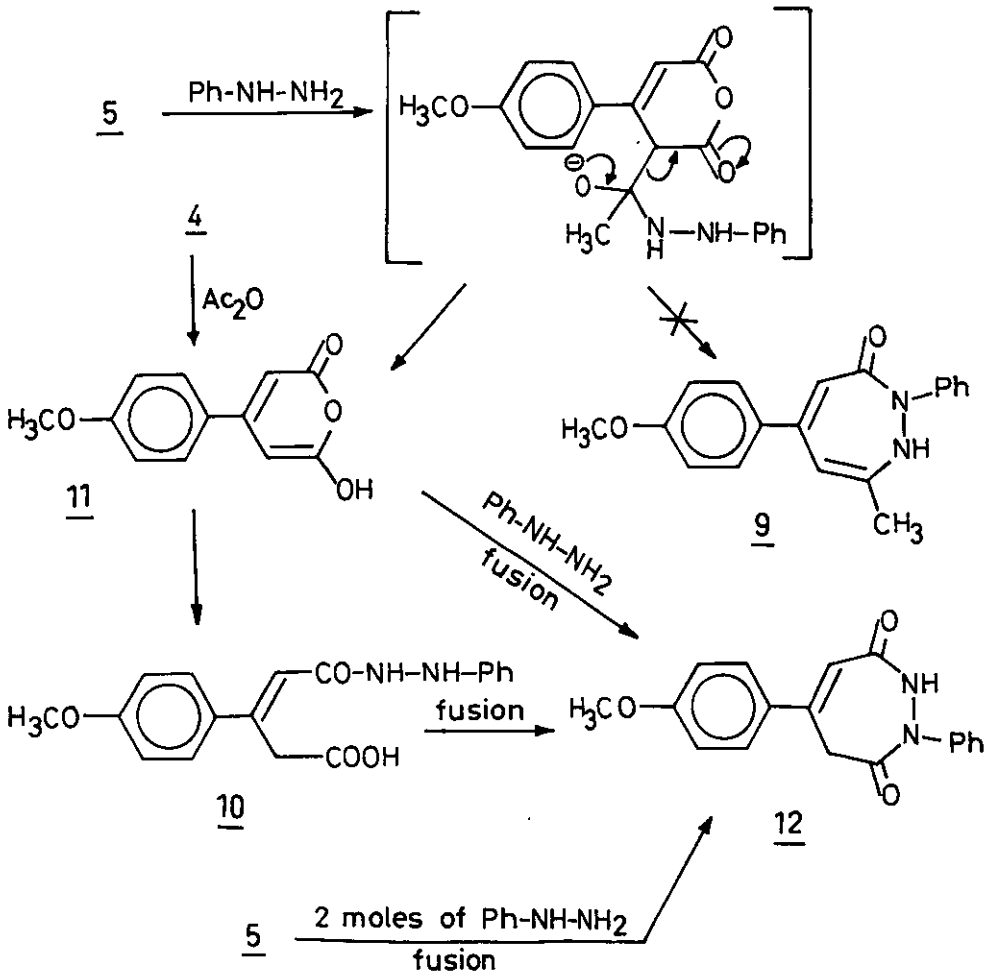
SCHEME-I



The reaction of 5 with phenyl hydrazine in benzene, however, took a different course and furnished 3-(4-methoxyphenyl)-2-pentenedioic acid-1-(2-phenyl) hydrazide (10), instead of the anticipated diazepinone 9. After the initial nucleophilic attack by phenyl hydrazine on the acetyl carbonyl carbon, both the nucleophilic centres of phenylhydrazine became impotent for the desired

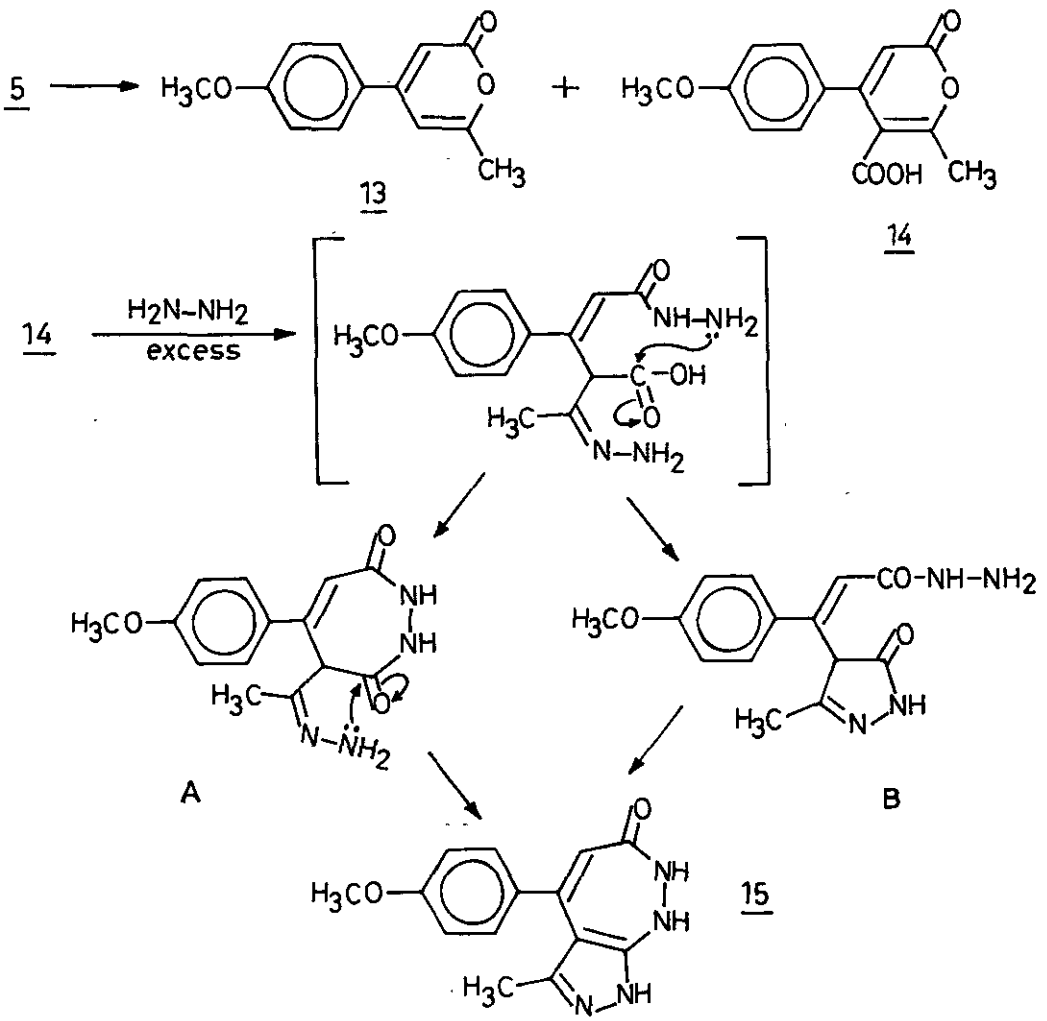
subsequent internal attack possibly due to the decreased basicity of the concerned nitrogen atoms and the steric interference of the phenyl ring. As a result it probably takes the other course as depicted in Scheme-1 to yield 4-(4-methoxyphenyl)-5H-pyran-2,6-dione (11) which with another mole of phenylhydrazine gave 10 which in turn could also be obtained by the direct reaction of phenylhydrazine with 11 in refluxing benzene. The anhydride 11 was in turn obtained[4] by treating 4 with acetic anhydride.

10 when heated to its fusion temperature underwent cyclization to yield 1,2-dihydro-5-(4-methoxy--phenyl)-1-phenyl-6H-[1,2]diazepin-3,7-dione(12), which was also obtained directly in one step from 5 or 11 and phenylhydrazine at high temperature but in low yield. Mass spectral fragmenta--tion patterns of 10 (M^+-18,308) were found to be identical with that of 12 for understandable reason. Cyclodehydration of 10, under the conditions in mass spectrometer, readily gives 12 which explains the similarity.



4-(4-Methoxyphenyl)-6-methyl-2H-pyran-2-one (13) and 5-carboxy-4-(4-methoxyphenyl)-2H-pyran-2-one (14) were also found to be important substrates for the preparation of diazepinones. These 13 and 14 were obtained[2] by the rearrangement of 5 in sulphuric acid. 13 on treatment with hydrazine hydrate gave diazepinone 8 which was also obtained from 5. The reaction of 14 with hydrazine resulted in the formation of two compounds which were separated by column chromatography. One of the products was 8, whereas, the other product was characterized as 1,2-dihydro-5-(4-methoxyphenyl) -6-methyl-8H-pyrazolo[3,4-c][1,2]diazepin-3-one (15). Under the reaction conditions, 14 partly undergoes decarboxylation to form 13 which gives 8. The remainder of 14 reacts with hydrazine to give 15 either through the intermediate A or B (Scheme-II). The intermediate A is more probable,

SCHEME-II



as B, which has pyrazolone aromatic ring is likely to resist attack of a nucleophile. It was interesting to note that at low temperature, there was no action of phenylhydrazine on 13 and 14; but at high temperature both 13 and 14 yielded the same product 1,2-dihydro-5-(4-methoxyphenyl)-7--methyl-1-phenyl[1,2]diazepin-3-one (9). The compound 15 was characterized by its IR and mass spectral molecular weight determination and elemental analysis. Its pmr spectrum could not be recorded due to its insolubility in most of the available solvents.

EXPERIMENTAL

All melting points were taken on Gallenkamp melting point apparatus and are uncorrected; ir spectra were determined in potassium bromide pellets with a Beckmann Acculab -10 spectrophotometer; nmr spectra were recorded on a Varian T 60 spectrometer (TMS as internal reference). Mass spectra were run on Varian Mat 112 S mass spectrometer at 70 eV energy.

1,2-Dihydro-5-(4-methoxyphenyl)-7-methyl[1,2]diazepin-3-one (8)

Hydrazine hydrate (1 ml) was added dropwise to the solution of 5 (1 mmole) in dry benzene (20 ml) under stirring at room temperature when white solid of 8 separated. The reaction mixture was further stirred for 2 h at room temperature. 8 was filtered, washed with benzene and recry--stallized from ethanol, (yield 72%); mp 172°C; ir : 3300 (NH), 3200 (NH), 1625 (CO) cm^{-1}; nmr (DMSO) : 2.43 (3H, s, CH_3), 3.80 (3H, s OCH_3), 6.12 (1H, s, C_6H), 6.58 (1H, s, C_4H), 7.00 and 7.68 (2H each, d, J = 8 H_z, ArH), 10.42 (2H, br s, exchangeable NH) ; ms M^+= 230; Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.80; H, 6.14; N, 12.17; Found : C, 67.71; H, 6.24; 12.24%.

8 was also prepared by refluxing the mixture of 13 (1 mmole) and hydrazine hydrate (1 ml) in ethanol (20 ml) for 2 h. The solvent was concentrated and cooled when 8 separated, (yield 65%).

3-(4-Methoxyphenyl)-2-pentenedioic acid 1-(2-phenyl)hydrazide (10)

A mixture of 5 (1 mmole) and phenyl hydrazine (2 mmoles) was refluxed in dry benzene (20 ml) for 1 h and cooled when 10 crystallized out. It was filtered and recrestallized from ethanol, (yield 80%) mp 170-171°C; ir : 3280 (NH), 3160-2840 (-C-NH-, OH), 1660 (CO), 1600 (CO) cm^{-1}; nmr (DMSO) : 3.80 (3H, s, OCH_3), 4.17 (2H, s, CH_2), 6.20 (1H, s, =CH), 6.53-7.63 (10H, m, ArH and NH), 9.66 (1H, s, CONH), 12.33 (1H, br s, COOH) ; ms M^+= 326; Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.30; H, 5.58; N, 8.59; Found : C, 66.29; H, 5.48; N, 8.66%.

10 was also prepared by refluxing the mixture of 11 (1 mmole) and phenyl hydrazine (1 mmole) in dry benzene (20 ml) for 1 h. The reaction mixture on cooling yielded 10, (yield 80%).

1,2-Dihydro-5-(4-methoxyphenyl)-1-phenyl-6H-[1,2]diazepin-3,7-dione (12)

10 (1 mmole) was heated in an oil bath at 180-185°C for 0.5 h. It was cooled and recrystallised from ethanol-DMF mixture, (yield 72%), mp 198-199°C; ir : 3340 (NH), 1720 (CO), 1680 (CO) cm^{-1}; nmr (DMSO) : 3.82 (3H, s, OCH_3), 4.22 (2H, s, CH_2), 6.05 (1H, s, =CH), 6.73-7.68 (10H, m, ArH and NH) ; ms M^+= 308; Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.24; N, 9.09; Found : C, 70.00; H, 5.20; N, 9.08%.

1,2-Dihydro-5-(4-methoxyphenyl)-6-methyl-8H-pyrazolo[3,-c][1,2]diazepin-3-one (15)

A mixture of 14 (1 mmole) and hydrazinehydrate (2 ml) was refluxed in ethanol (20 ml) for 2 h. The alcohol was removed in vacuo. The residue containing 8 and 15 was chromatographed (silica gel, ethyl acetate). 15 was eluted with ethyl acetate and 8 (yield 35%) was eluted with ethanol. 15 was recrystallized from ethanol, (yield 23%); mp 200-201°C; ir : 2980 (NH); 2940 (NH); 2840 (NH); 1600 (CO) cm^{-1}; ms M^+= 270; Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.20; H, 5.23; N, 20.73; Found : C, 62.28; N, 20.98%.

1,2-Dihydro-5-(4-methoxyphenyl)-7-methyl-1-phenyl[1,2]diazepin-3-one (9)

A mixture of 14 (1 mmole) and phenyl hydrazine (1 mmole) was refluxed in dry xylene (20 ml) for 6 h. The reaction mixture on cooling yielded 9 which was recrystallized from xylene, (yield 65%); mp 211-212°C; ir : 3240 (NH); 1650 (CO), cm^{-1}; nmr ($CDCl_3$) : 2.40 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.33 (1H, s, C_6H), 6.57 (1H, s, C_4H), 6.68-7.60 (10H, m, ArH and NH) ; ms M^+ = 306; Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.48; H, 4.93; N, 9.15; Found : C, 74.58; H, 4.87; N, 9.24%.

9 was also prepared by refluxing the mixture of 13 (1 mmole) and phenylhydrazine (1 mmole) in dry xylene (20 ml) for 6 h, (yield 51%).

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