Synthesis of some derivatives of dimedone, gamma pyrone and barbituric acid.

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ABSTRACT

Aim: Dimedone, gamma pyrone and barbituric acid and their derivatives have also been found to be very important from their application point of view. Thus our aim was to prepare more derivatives from them. Method: Dimedone, gamma pyrone and barbituric acid have been treated with dimethyl sulphoxide and acetic anhydride reagent under varying temperature conditions in order to get more compounds. Result: The interaction of DMSO-Acetic anhydride with Dimedone (1) gives (2) and (3), with gamma pyrone (5) gives (6), (7), and with barbituric acid (10) gives (11) and (12). Conclusion: A number of compounds were synthesized.

KEYWORDS: Acetic anhydride, barbituric acid, ß-diketones, Dimedone, DMSO, gamma pyrone, synthetic methods.

1. INTRODUCTION

The 5,5-dimethyl-1,3-cyclohexanedione (dimedone) is one of the most studied ß-diketone specially because of the fact that its derivatives have been found to be fungicides and herbicides1 besides having other applications.2-4 4-hydroxy-6-methyl-2H-pyran-one (triacetic acid lactone or gamma pyrone) is an aliphatic analogue of hydroxycoumarin with which it shares similar chemical properties. Derivatives of gamma pyrone acts as an inhibitor or interleukin-1 ß inventory enzyme,3 as intermediates for dyes and pharmaceuticals4 and as potential anti-cancer drugs.5 The literature shows no reference about reaction between this interesting molecule and DMSO acetic anhydride. Barbituric acid generally synthesized through interaction of diethyl malonate and urea in the presence of sodium ethoxide has also been synthesized, using same ingredients, in commercial microwave even within a few minutes.6 Barbituric acid derivatives have antitumor and antimetastatic activity.7,8 5,5-methylene-bis-barbituric acid and its derivatives have also been synthesized and their metal salts used as pigments.9 Non-sedating barbituric acid derivatives have been used as neuroprotection and prevention of neuronal damage.10 Keeping in view the importance of these compounds, it was worth trying to get more derivatives from them and the compounds which we synthesized have been reported.

2. MATERIALS AND METHODS

2.1. Reaction of dimedone with DMSO-acetic anhydride.

2.1.1. At room temperature:

A mixture of dimedone (4.5g), DMSO (26ml) and acetic anhydride (13 ml) was kept at room temperature for three days. Jelly like substance which separated out on the addition of distilled water was extracted with ethyl acetate, organic layer washed, dried and the solvent evaporated. Chromatography of the residue in benzene and benzene-ethyl acetate afforded spiran (3), which was crystallized from ethanol.

Data

Spiran (3): (2.390g), m.p 207°C. IR (KBr): 1660, 1740, 1770 and 3000 cm⁻¹; ¹H NMR (CDCl₃, 90 MHz): δ 2.96 (2H, s, Allylic methylene), δ 2.53 (2H, s, Dihydrofuran methylene), δ 2.29 (6H, s, -CH₂CO-), δ 1.26 (3H, s, methyl protons), δ 1.20 (6H, s, methyl protons), δ 1.03 (3H, s, methyl protons); (m/z): 290 (M⁺), 206, 178, 83 (base peak). (Found C, 71.67; H, 7.80%. C₁₇H₂₂O₄ required C, 70.34; H, 7.58%).

2.1.2. At water bath temperature:

Dimedone (4.5g) was taken in DMSO (26ml) and acetic anhydride (13 ml) was kept at room temperature for three days. Jelly like substance which separated out on the addition of distilled water was extracted with ethyl acetate, organic layer washed, dried and the solvent evaporated. Chromatography of the residue in benzene and benzene-ethyl acetate afforded spiran (3), which was crystallized from ethanol.

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2.1.3. At boiling water bath temperature:

Dimedone (4.5g) was taken in DMSO (40ml) and acetic anhydride (20 ml) was kept on a boiling water bath for 24 hours. Workup of the reaction mixture and chromatography over silica gel using benzene and benzene-ethyl acetate as eluent afforded 2,2-methyl-ene-bis-5,5'-methyl-ene-bis-5,5'-dimethyl-1,3-cyclohexanedione (2), on crystallization from ethanol.

Data

2,2-methyl-ene-bis-5,5'-methyl-ene-bis-5,5'-dimethyl-1,3-cyclohexanedione (2): (3.207g), m.p 193°C. IR (KBr): 1660, 1740, 1770 and 3000 cm⁻¹; ¹H NMR (CDCl₃, 90 MHz): δ 2.96 (2H, s, Allylic methylene), δ 2.53 (2H, s, Dihydrofuran methylene), δ 2.29 (6H, s, -CH₂CO-), δ 1.26 (3H, s, methyl protons), δ 1.03 (3H, s, methyl protons); (m/z): 570 (M⁺), 386, 318, 130 (base peak). (Found C, 71.67; H, 7.80%. C₁₇H₂₄O₄ required C, 70.34; H, 7.58%).
cyclohexanedione (2): m.p. 184°C. IR (KBr): 1350, 1420, 1550-1600 and 2840 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 90 MHz): \(\delta\) 3.27, (2H, s, \(-\text{CH}_2\)), \(\delta\) 2.4 (8H, S, \(-\text{CH}_2\)), \(\delta\) 1.15 (12H, s, \(-\text{CH}_3\)); \(m/z\): 292 (M\(^+\)), 277, 165, 124 and 83. (Found C, 68.32; H, 8.33%. C\(_{16}\)H\(_{12}\)O\(_4\) requires C, 69.86; H, 8.21%).

2.1.3. With preheated DMSO-acetic anhydride: A mixture of DMSO (20ml) and of acetic anhydride (10ml) was heated on water bath for two hours. To this preheated mixture dimedone (3g) was added and it was allowed to stand at water bath temperature for 16 hours. Usual workup and chromatography afforded only (2) as pure component, yield 1.478g.

2.1.4. At 150°C: A solution of dimedone (4g), DMSO (20ml) and acetic anhydride (10 ml) was maintained at 150°C in an oil bath for 10 hours. Addition of water (200 ml) to the cooled reaction mixture afforded oil which on extraction with ethyl acetate and chromatography over silica gel in benzene - ethyl acetate mixture did not give any pure compound in desirable amounts.

2.2. Reaction of gamma pyrone with DMSO-acetic anhydride.

2.2.1. At room temperature: A mixture of gamma pyrone (3.7g), DMSO (15ml) and acetic anhydride (7.5ml) was kept at room temperature for 8 days. During this period a crystalline material separated out from the reaction mixture. It was filtered and washed with dry benzene but its major portion got dissolved in it and only a small amount was left on the filter paper which was characterized as 3-methylsulphuranylidene-6-methyl-2H,4H-pyran-2,4-dione (6). The benzene washings on dilution with petroleum ether afforded a more of the crystalline compound (6), combined yield 2.28g.

Data
3-methylsulphuranylidene-6-methyl-2H, 4H-pyroano-2, 4-dione (6): m.p. 182°C. IR (KBr): 1390, 1460-1600 and 2850 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 90 MHz): \(\delta\) 5.7 (1H, s, -C-CH-CO), \(\delta\) 3.1 (6H, s, -CH\(_2\)), \(\delta\) 2.1 (3H, s,-CH\(_3\)), \(m/z\): 186 (M\(^+\)), 171, 139, 111, 102 and 87 (base peak). (Found C, 51.25; H, 5.52 %. C\(_{12}\)H\(_{16}\)O\(_4\)S requires C, 51.6; H, 5.37 %).

2.2.2. With preheated DMSO-acetic anhydride: DMSO (15ml) and acetic anhydride (7.5ml) were heated on water bath for two hours and to it was added gamma pyrone (2.2g). The reaction mixture was maintained at this temperature for 28 hours. Upon distillation of distilled water turbidity appeared which ultimately turned jelly-like. It was extracted with ethyl acetate, the organic layer washed several times with water, dried over anhydrous sodium sulphate and solvent removed. Chromatography of the residue over silica gel and elution with benzene and benzene-ethyl acetate afforded 6-methyl-3-

3-methylene-bis-2H-pyran-2-one (7), which was crystallized from benzene.

Data
6-methyl-3, 3-methylene-bis-2H-pyran-2-one, (7): m.p. 245-246°C. IR (KBr): 1350, 1460-1600 and 2850 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 90 MHz): \(\delta\) 5.7 (1H, s, -C-CH-CO), \(\delta\) 3.1 (6H, s, -CH\(_2\)), \(\delta\) 2.1 (3H, s,-CH\(_3\)), \(m/z\): 271 (M-47), 241, 212, 166, 149, 137, 122 105  and 77.

2.3. Reaction of barbituric acid with DMSO-acetic anhydride.

2.3.1. At Room Temperature. DMSO (2ml) and acetic anhydride (1ml) was added to barbituric acid (0.2g) and the reaction mixture was kept at room temperature for five days. 5-Methyl sulphuranylidene-2,4,6(1H,3H)-pyrimidinetrione (11), which separated out from the reaction mixture was filtered, washed with dry benzene and crystallized from water, yield 0.16g, m.p. 237°C. It gave positive test for sulphur. Its identity was confirmed through direct comparison (ir, pmr, mass data reported in literature).

2.3.2. At water bath temperature: DMSO (20ml) and acetic anhydride (10ml) was added to barbituric acid (5g) and the reaction mixture was kept on water bath for two hours. The solid which separated out from the reaction mixture was filtered and washed with dry benzene. It was found to be identical with (11), yield 0.275g.

2.3.3. With preheated DMSO-acetic anhydride: A mixture of DMSO (20 ml) and acetic anhydride (10 ml) was heated on water bath for two hours. To it was added barbituric acid (5g) and the reaction mixture was allowed to stand at water bath temperature for about eight hours. The solid which separated out from the reaction mixture was filtered and washed with benzene. It was found to be identical with (11). On addition of chloroform to the mother liquor, a solid separated out which became sticky after some time. It was filtered, washed with chloroform and crystallized from water to give 5(methylsulfonyl)aminomethylidyne-4,5-dihydrofuran-3-carboxylic acid (5g) and the reaction mixture was kept at room temperature for five days. 5-Methyl sulphuranylidene-2,4,6(1H,3H)-pyrimidinetrione (11), which separated out from the reaction mixture was filtered, washed with dry benzene and crystallized from water, yield 0.16g, m.p. 237°C. It gave positive test for sulphur. Its identity was confirmed through direct comparison (ir, pmr, mass data reported in literature).
3. RESULTS AND DISCUSSIONS

3.1 Reaction of DMSO-Acetic anhydride with Dimedone.

At room temperature the reaction between dimedone and DMSO-Acetic anhydride reached completion in three days. Distillation of the reaction mixture under reduced pressure to remove excess DMSO-acetic anhydride, in order to get the corresponding ylide failed. Since not even a trace of ylide could be detected, the subsequent reaction mixture was worked up through addition of water and extraction with appropriate solvent. Chromatography of the reaction mixture over silica gel afforded only one pure compound (3) m.p 207°C in substantial yields. Its ir spectrum shows strong carbonyl absorption at 1740 cm⁻¹ with a shoulder of less intensity at 1770 cm⁻¹ and a still prominent band at 1660 cm⁻¹. On the basis of its mass spectrum and elemental analysis its molecular formula was found to be C₁₇H₂₂O₄, indicating dimerisation of the dimedone molecule. It can be presumed that the dimeredone reacts initially with DMSO-acetic anhydride to give 2,2'-methylene-bis-dimedone (2) (Mₒ.formula, C₁₇H₂₂O₄) which then undergoes dehydrogenation to give a compound (3) having desired mass and molecular formula. Further, (3), was found to be the correct structure for this compound on the basis of its spectral data. The same compound is reported to have been formed on interaction of dimedone with formaldehyde and iodine and the reported spectral data is identical with that of our compound and, therefore, leaves no doubt about its assigned structure.

Formation of this compound has not been reported from DMSO-acetic anhydride reaction. Conversion of 3, 3'-methylene-bis-dimedone to (3) can be due to the more stable enol tautomers of the dimedone moieties. Hydroxyl of the one can form sulphonium salt (4) and that of other participates in oxidation step to give spiran (3) with elimination of dimethyl sulphide (Scheme-2). At water bath temperature the reaction between dimedone and acetic anhydride results in the formation of two products and complete utilization of the starting material occurred in 24 hours. The major product in about 80% yields was identified as the spiran (3). Other product, m.p 184°C, formed in about 20% yield was identified as 3,3'-methylene-bis-dimedone (2) on the basis of its spectral data. Its mass spectrum shows M⁺ at m/z 277, 165 and 83. The ir spectrum shows carbonyl bands at lower frequency as compared to dimedone and is similar to the one observed in the case of 4-hydroxycoumarin, showing C=O stretching bands at 1685 and 1720 cm⁻¹, whereas in dicoumarol the corresponding bands are found as multiplets between 1620 and 1655 cm⁻¹. The proton magnetic resonance spectrum shows a singlet equivalent to twelve protons for four methylene groups of the dimeone nuclei and a singlet at δ 3.27 equivalents to two protons for the central methylene group. All of these are in full agreement with this structure.

Isolation of this compound clearly establishes its intermediacy during the formation of compound (3). With preheated DMSO-acetic anhydride, an excellent source of formaldehyde, the dimedone gives exclusively 3,3'-methenyl-bis-dimedone like all other ß-diketones.

Scheme 1- Mechanism for the formation of (3) from (1).

Scheme 2- Mechanism for the formation of (3) from (2).

3.2. Reaction DMSO-Acetic anhydride with gamma pyrone

At room temperature triacetic acid lactone (5) reacts completely with DMSO-acetic anhydride in a week’s time and furnishes a single crystalline compound, m.p 182°C, on usual workup. It was found to have sulphur and was water soluble. On the basis of its spectral data and chemical behaviour, the compound was identified as the ylide (6). The ir spectrum shows a broad carbonyl band between 1640-
1660 cm\(^{-1}\), a singlet equivalent to three protons at \(\delta\) 2.1 for allylic methyl, a singlet at \(\delta\) 3.1 for two methyl groups on sulphur, a singlet of one allylic proton at \(\delta\) 5.7 in its pmr spectrum and strong M\(^+\) at m/z 186, important fragments at m/z 171 (M-CH\(_3\)), 139 (M-SCH\(_3\)), 102 (on RDA fragmentation) and 87 in its mass spectrum and these are all in full agreement with this structure (Scheme-3).

Scheme 3- Mechanism for the formation of (6) from (5).

Reaction with pre-heated DMSO-acetic anhydride, however, afforded a pure crystalline compound, m.p. 245-246\(^\circ\)C in good yields. Its ir spectrum in the carbonyl region (1630-1660 cm\(^{-1}\)) was comparable with that of dicoumarol aromatic stretching frequencies. The pmr spectrum shows sharp singlets at \(\delta\) 2.35 (for six protons) \(\delta\) 3.60 and \(\delta\) 6.10 (for two protons each) which can easily be assigned to two allylic methyl protons, doubly allylic methylene protons and two olefinic protons respectively, if the compound is 3,3-methylene-bis-triacetic acid lactons (7), an analogue of dicoumarol. Its identity was further confirmed through direct comparison with an authentic sample of (7) obtained on direct treatment of triacetic acid lactone with formalin in ethyl alcohol. Formation of this compound (7) in DMSO-acetic anhydride reaction especially with pre-heated reagent takes place on similar lines as discussed earlier and again confirming our assumption that the pre-heated DMSO-\(\beta\)-diketone reagent is an excellent alternative source of formaldehyde and can be useful in reactions requiring anhydrous conditions. The 3,3-methylene-bis-triacetic acid lactone (7), once formed should undergo oxidative cyclisation to give (8), which having one reactive \(\beta\)-keto-lactone ring should suffer hydrolysis and decarboxylation to give (9). This again, being a \(\beta\)-diketo compound and having a lactone ring, is susceptible to further reaction with DMSO-Ac\(_2\)O and acetate ion catalyzed degradations. Because of this the reaction of triacetic acid lactone with DMSO-acetic anhydride at higher temperature (water bath and above) led to extensive decomposition and even after repeated chromatography, sufficiently pure compounds could not be isolated (Scheme-4).

Scheme 4 - Mechanism for the conversion of (5) to (7) and its extensive decomposition.

3.3 Reaction DMSO- Acetic anhydride with barbituric acid.

Reaction of barbituric acid (10) with DMSO/DCC\(^{12}\) and DMSO-acetic anhydride\(^{13}\) has been reported to give the corresponding ylide (11). The reaction was repeated and (11) was the sole product obtained at room and water-bath temperatures. Its identity was confirmed through comparison of data reported in literature. The reaction between barbituric acid and DMSO-acetic anhydride at higher temperatures (150\(^\circ\)C), however, afforded an amorphous compound, m.p. 159\(^\circ\)C, in about 50\% yields and responded positively when tested for the presence of sulphur and carboxylic acid. Its ir spectrum shows multiplets of carbonyl stretching bands between 1660-1740 cm\(^{-1}\). The mass spectrum shows a peak at highest mass value m/z 271 indicating formation of 5,5-dicarbonyl derivatives, the expected product of DMSO-acetic anhydride and \(\beta\)-diketone reactions, and its oxidative degradation coupled with methythiomethylation. Of the various possible structures, (12) was found to be the most plausible one. Its formation can be explained on the basis that 5,5-dimethyl-bis-barbituric acid, formed during this reaction, undergoes oxidative cyclization like dicoumarols to give (13) which suffers acetoxylation of both barbiturate rings and also methylthiomethylation (Scheme 5). The multiplets of carbonyl bands in its ir spectrum can be assigned to \(\alpha\)-\(\beta\)-unsaturated \(\alpha\)-esters and various amide carbonyls. The pmr spectrum in DMSO-d\(_6\) is not well resolved but clear singlets in the aliphatic region at \(\delta\) 2.15 equivalents to three protons, and at \(\delta\) 2.60 and \(\delta\) 3.40 equivalents to two protons each can readily be assigned to \(-\text{S-CH}_2-\) furan methylene and \(-\text{CH}_2-\text{S-}\) protons respectively. As expected the M\(^+\) at m/z 318 in its mass spectrum is missing and the peak at highest m/z 271 (M-47) can arise through facile loss of \(-\text{S-CH}_3\) group. Other important peaks at m/z 241 can arise through loss of \text{CH}_3\_\text{SCH}_2\_\text{NH}_2 or urea plus water from the parent molecule (Scheme-5).
4. CONCLUSION
Keeping in view the importance of dimedone, gamma pyrone and barbituric acid, they were treated with dimethyl sulphoxide and acetic anhydride reagent, a very versatile reagent and six compounds (2), (3), (5, 6), (7), (11) and (12) were formed which can be evaluated for medicinal uses.

5. REFERENCES

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