SYNTHESIS OF DIMERIC BARBITURATES

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Abstract

The dimerisation reaction of 1,3-diphenyl barbituric acid 1 and 1,3-diphenyl 2-thiobarbituric acid 3 has been studied. Alkaline solution of these acids when treated with vinyl acetate, yielded 5,5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenly)-2,4-dioxo pyrimidine 2 and 5,5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenly)-4-oxo-2-thio pyrimidine 4 respectively. The structures of these compounds have been confirmed from their spectral and analytical data.

Introduction

A large number of barbiturate and thiobarbiturate derivatives have been reported to exihibit a broad spectrum of biological activities, such as anticonvulsant [1,2], sedative and hypnotic [3-6], antibacterial[7], insecticidal [8,9] and antineoplastic activities[10]. In addtion, synthetic studies of fused pyrimidines have been documented extensively because of their structural diversity and to carry out further for the study of above activities. We have recently reported [11,12] the synthesis of novel pyranobis quinolines, pyranobis benzopyrans and benzopyrano-pyranoquinolines through the intermediate quinone methides. In continuation of our ongoing interest in the preparation of dimerized product, we now report the synthesis of 5,5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenly)-2,4-dioxo pyrimidine 2.

Experimental

General Information

Thin layer chromatography was used to access reactions and purity of products. Melting points were determined on a Boetius Microheating Table and Mettler-FP5 Melting-Point apparatus and are uncorrected. IR spectra were recorded in Shimadzu -8201 FT instrument in KBr disc and only noteworthy absorption levels(reciprocal centimeter) are listed. ^{1}H-NMR spectra were recorded in a AMX-400 MHz spectrometer in DMSO-d_6 solution; chemical shifts are expressed in ppm(δ) relative TMS, coupling constants (J) in Hz and signal multiplicities are represented by s(singlet), d(doublet), q(quartet) and m(multiplet). Mass spectra were recorded on a Jeol - 300 mass spectrometer .

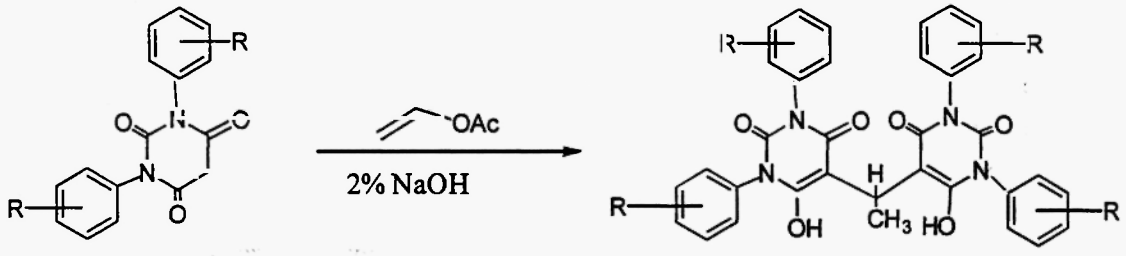
General Procedure

1,3-Diphenyl barbituric acid(0.002mole) or 1,3-Diphenyl-2-thiobarbituric acid acid (0.002mole) was stirred at room temperature in 100 ml of 2% sodium hydroxide solution taken in a 250ml round bottom flask. To the alkaline solution vinyl acetate (0.02 mole) was added and the stirring was continued for 5-6 hours. The precipitated product was filtered carefully, washed with water and dried. The crude product was purified by recrystallising from $CHCl_3$-CH_3OH solution.

Results and Discussions

When a solution of 1,3-diphenyl barbituric acid in 2% sodium hydroxide was treated with vinyl acetate at room temperature, a yellow coloured solid separated out. It was filtered and recrystallised from $CHCl_3$-CH_3OH solution (Yield: 85%; M.P.:182.5 °C). Its IR spectrum registered >C=O absorption peaks at 1685 cm^{-1} and 1649cm^{-1}, -OH absorption in the region 3290-3650cm^{-1} and C-N peak at 1595 and 1544 cm^{-1}. The ^{1}H-NMR spectrum of the compound exihibited a doublet at δ2.5 which might be ascribed to methyl protons, a quartet at δ 7.1 was accouontable to methine proton. The low field shift of the methine proton may be due to the presence of >C=O and >C-OH groups adjacent to the proton13. All the twenty aromatic protons gave multiplet between δ 6.95 and 7.6. A singlet at δ 8.6 was assigned to -OH group. The mass spectrum illustrated the molecular ion peak at m/z 586. The elemental analysis (CHN) agreed well with the molecular formula $C_{34}H_{26}N_4O_6$.All the above spectral data accredited the compound 2a as 5,5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenly)-2,4-dioxo pyrimidine(scheme 1)

Scheme 1

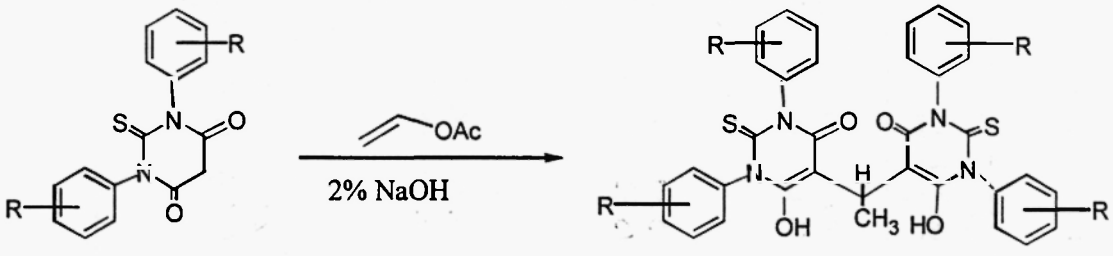


1 2

1,2 a: R = H
b: R = 2-CH_3
c: R = 4-CH_3
d: R = 2 – OCH_3

Having achieved in the dimierisation reaction of 1,3-diphenyl barbituric acids, we extended our reaction technique for 1,3-diphenyl 2-thiobarbituric acid also(Scheme 2). The products obtained were substantiated through IR, ^{1}H-NMR , mass and elemental analysis and were given in the table 2.

Scheme 2



3 4

3,4 a: R = H
b: R = 2-CH_3
c: R = 4-CH_3
d: R = 2 – OCH_3

Table 1. Physical and spectral data of 5, 5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenyl)-2,4-dioxo pyrimidine 2

Compound	Yield (%)	M.P. (°C)	IR(cm^{-1})	MS(70eV) m/e (m^+)	Molecular Formula	Analysis Found(Calcd.) C	H	N	^{1}H-NMR (DMSO-d6)δ/ppm
2a	85	182.5	3200-3600(OH), 1695,1649(C=O)	586	$C_{31}H_{25}N_4O_4$	69.62 (69.58)	4.44 (4.43)	9.56 (9.57)	2.50(d,3H,CH_3), 7.1(q,1H,-CH-), 6.9-7.9(m, 20H, Ar-H), 8.6(s,2H, 2XOH)
2b	56%	214.8	3200-3450(OH), 1647,1614(C=O)	642	$C_{38}H_{34}N_4O_5$	71.03 (71.13)	5.30 (5.32)	8.72 (8.73)	2.2(d,3H CH_3), 2.5(s,12H,4xCH_3), 6.8(q,1H,-CH-), 7-8.0(m,16H,Ar-H), 8.4(s,2H,2xOH)
2c	60	134.1	3250-3500(OH), 1695,1647(C=O)	642	$C_{38}H_{34}N_4O_6$	71.03 (71.09)	5.30 (5.29)	8.72 (8.75)	2.3(d,3H,CH_3), 2.5(s,12H,4xCH_3), 6.6(q,1H,-CH-), 7.1-8.2(m,16H,Ar-H), 8.3(s,2H,2xOH)
2d	62	210.3	3250-3600(OH), 1697,1645(C=O)	706	$C_{38}H_{34}N_4O_{10}$	64.59 (64.62)	4.82 (4.85)	7.93 (7.91)	2.5(d,3H,CH_3), 3.7(s,12H,4xOCH_3), 6.8(q,1H,-CH-), 7.0-8.1(m,16H,Ar-H), 8.8(s,2H,2xOH)

Table 2. Physical and spectral data of 5, 5'-(methyl)-methylene-bis-(6-hydroxy-1,2,3,4-tetrahydro-1,3-diphenyl)-4-oxo-2-thio pyrimidine 4

Compound	Yield (%)	M P. (°C)	IR(cm^{-1})	MS(70eV) m/e(m^+)	Molecular Formula	Analysis Found(Calcd.) C	H	N	^{1}H-NMR(DMSO-d_6)δ/ppm
4a	50	300	3200-3600(OH), 1600(C=O), 1323(C=S)	618	$C_{34}H_{26}N_4O_4S_2$	66.02 (66.08)	4.21 (4.23)	9.06 (9.08)	2.4(d,3H,CH_3), 6.8(q,1H,-CH-), 7.0-8.1(m,16H,Ar-H), 9.2(s,2H,2xOH)
4b	64	239	3250-3600(OH), 1612(C=O), 1323(C=S)	674	$C_{38}H_{34}N_4O_4S_2$	67.66 (67.69)	5.05 (5.01)	8.31 (8.29)	2.3(d,3H,CH_3), 2.4(s,12H,4xCH_3), 6.7(q,1H,-CH-), 6.9-7.8(m,16H,Ar-H), 9.5(s,2H,2xOH)
4c	48	172	3150-3500(OH), 1615(C=O), 1323(C=S)	674	$C_{38}H_{34}N_4O_4S_2$	67.66 (67.63)	5.05 (5.03)	8.31 (8.32)	2.2(d,3H,CH_3), 2.5(s,12H,4xCH_3), 6.9(q,1H,-CH-), 7.0-7.9(m,16H,Ar-H), 9.6(s,2H,2xOH)
4d	62	113	3150-3600(OH), 1620(C=O), 1325(C=S)	738	$C_{38}H_{34}N_4O_8S_2$	61.79 (61.82	4.61 (4.63)	7.59 (7.60)	2.3(d,3H,CH_3), 3.9(s,12H,4xOCH_3), 6.7(q,1H,-CH-), 7.0-8.2(m,16H,Ar-H), 9.5(s,2H,2xOH)

References

1. L.S. Goodman and A. Gilman, The Pharmacological basis of therapeutics(McGrow-Hill New Delhi), 358, (1991).
2. A.N. Osman, M.M. Kandel, IJC, 35B, 1073(1996).
3. Andres Goth, Medical pharamacology(The CV Mosby Company, Saint Louis), 243(1976).
4. W.O. Foye, Principles of Medicinal Chemistry(Lea and Febiger, London), 155,(1989).
5. F.H. Meyer, E. Jawetz and A. Goldfield, Review of Medical Pharamacology(Lange Medical Publications, Los Altos, California, 222,(1976).
6. Wilson and Gisvold's, Textbook of organic medicinal and pharmaceutical chemistry (J.B. Lippneaur Company, Phildelphia, New York),368, (1991).
7. J.A. Bares, N.J. Kurlick, S.E. Shaffer and M.G. Varner, J. Med. Chem. Chim. Ther, 15, 571,(1980); Chem. Abstr, 94,1981 156853g.
8. W. Kraemer, W. Draber, I. Hammanin and H. Scheinpt Lieg, Chem. Abstr., 84,1976,4992g.
9. Y. Hirona, H. Ishikawa, I. Iwataki, M. Swaki and O. Nomura, Ger Offen, 25244578, 11 Dec 197, Chem. Abstr., 84, 1976 121891i..
10. A. Krewtzberger and E. Kreutzberger , Arch Pharm, 318(9),821,(1985).
11. C. Balasubramanian , K. Kumaraswami, N. Dharmaraj and P.S. Mohan, Ind. J. Chem., 32B,460(1993).
12. C. Balasubramanian, M. Sekar and P.S. Mohan, Ind. J. Chem., 35B, 1225(1996).
13. V. K. Ahluwalia and Umashankar Das, Ind. J. Chem., 35B, 852(1996).

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