Pergamon

Tetrahedron, Vol. 52, No. 30, pp. 10147-10158, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00537-6

Peculiar Reaction Behaviour of Barbituric Acid Derivatives Towards Aromatic Amines.

Hanafi H. Zoorob, Mohamed M. Abou - El Zahab, Mamdouh Abdel - Mogib and Mohamed A. Ismail*

Faculty of Science,. Al - Mansoura University, Chemistry Department, Al - Mansoura, A. R. Egypt

Abstract: 5-Benzoylethyl barbituric acid derivatives **2a-c** were prepared as useful precursors for the synthesis of pyrimidine fused heterocycles. Their behaviour as 1,5-diketocompounds towards aniline derivatives afforded the pyrimidoquinoline derivatives **6a-e**. On the other hand, fusion of o-substituted anilines with 1,3-dimethyl barbituric acid derivatives **8a,b** gave the corresponding benzazoles **10a-e**. Furthermore, the reaction of 1,3-dimethyl barbituric acid (**1**) with catechol/$K_3[Fe(CN)_6]$ or β-ketoester (**19**)/$SiCl_4$ gave the benzofuro adduct **13a** and the diphenylphenyl barbituric acid derivative **18**, respectively Copyright © 1996 Elsevier Science Ltd

Pyrimidine annelated heterocycles belong to an important class of biologically active compounds. These compounds such as xanthines and other purines contain a characteristic pyrimidine-2,4-dione ring system. The importance of purine bases and analogous compounds in pharmaceutical and biological fields is well known.[1,2]

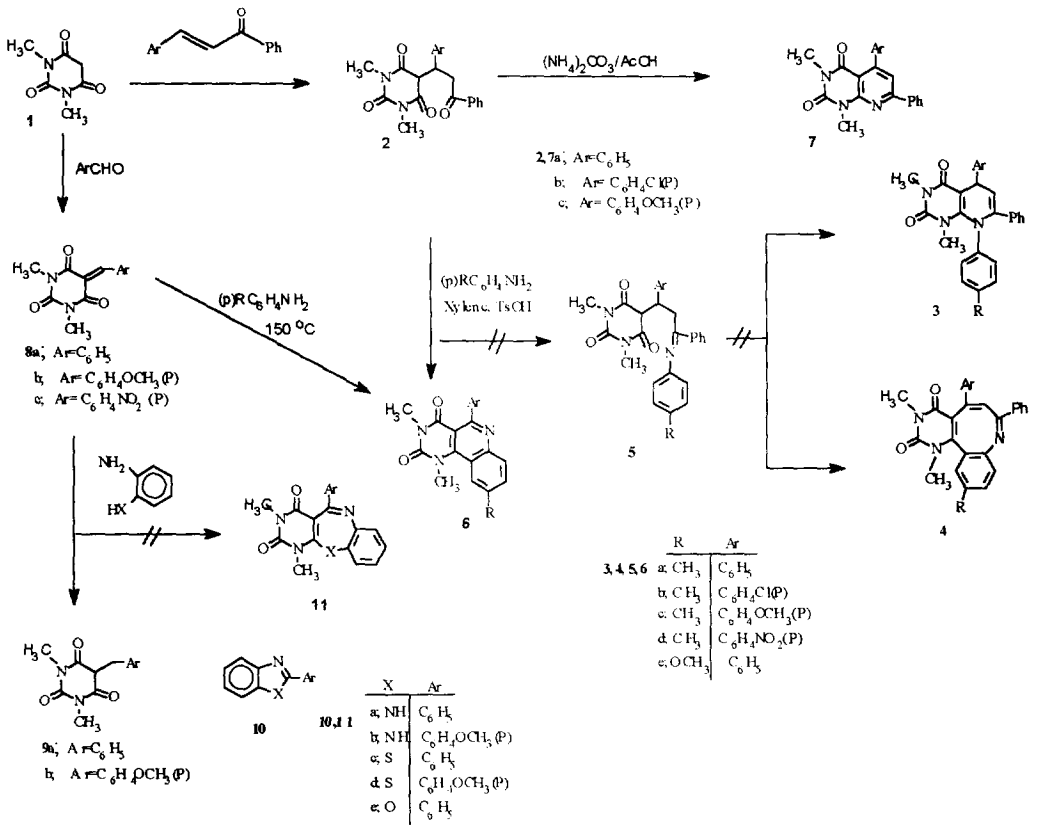
With the development of clinically useful pyrimidine-based anticancer (5-Fluorouracil [3]) and antiviral drugs (AZT, BVDU[4]), there has been noticeable interest in the synthetic manipulations of uracils.[5,6,7]

This persuaded us to investigate the C_5 and C_6 reactivities the oxo-analogues of uracil, e.g., barbituric acid and its derivatives, as centers of heteroannulation. The synthetic exploitation of these C_5 and C_6 reactivities is considered to be an important undeveloped field in view of the great variety of potential products.

Therefore, 5-benzoylethyl barbituric acid derivatives **2a-c** were prepared as useful precursors for the synthesis of pyrimidine fused heterocycles. Thus the base catalysed addition of 1,3-dimethyl barbituric acid **(1)** to appropiate α,β-unsaturated ketones afforded the Michael adducts **2a-c**. Their structures were confirmed by elemental analysis, IR and ^{1}H-NMR spectra. The ^{1}H-NMR spectrum of **2a** not only confirms the structure, but also indicates its stereochemistry. The small coupling of 4Hz between H-5 and H-7 of compound **2a** suggested the eclipsed conformation of H-5 and H-7 in this compound.

In view of the significant therapeutic value of pyridines it was considered worthwhile to incorporate pyridine moieties into the C_5/C_6 position of the pyrimidine nucleus. To this end, it seemed desirable to investigate the reactivity of benzoylethylbarbituric acids **2a-c**, 1,5-diketo compounds, towards primary amines.

Unexpectedly, the reaction of diketones **2a-c** by refluxing them in xylene with aniline derivatives in the presence of a catalytic amount of p-toluene sulphonic acid does not give either the hoped for



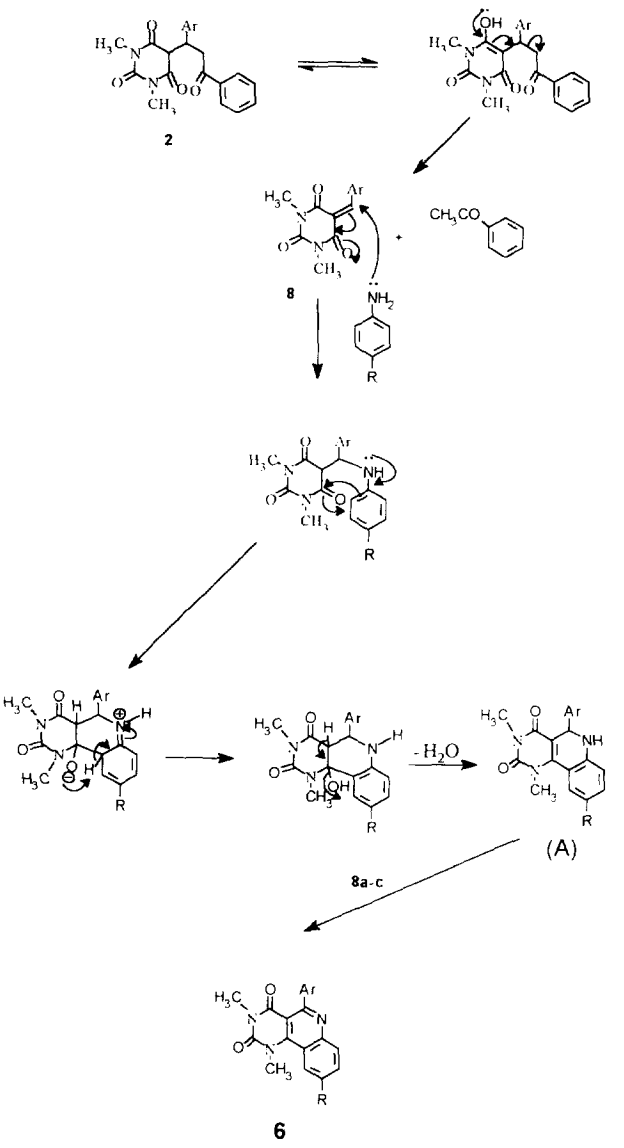
Scheme (1)

pyridopyrimidines **3a-c** or pyrimidoazocines **4a-c** through cyclization of the expected intermediate schiff bases **5a-c**. Instead, the pyrimidoquinoline derivatives **6a-c** were produced. Their structures were confirmed from the elemental analyses as well as the spectral data. The ^{1}H-NMR spectrum of **6a** does not show the expected AA` BB` system for a p-substituted benzene ring; however, it showed a 1,2,4-trisubstituted benzene moiety indicated by presence of three proton signals at δ 7.13 br s (attributed to H-10), 7.92 *d* (J=8.5 Hz) (attributed to H-7) and 7.62 *dd* (J=8.5, 2 Hz) (attributed to H-8). The molecular ion peak in the mass spectrum of 6a was 331 (m/z). Also, the mass spectrum of 6b showed a molecular ion peak at (m/z) (rel. int.) 368, 366 (33:100, i.e., 1:3).

The probable mechanism for production of the pyrimidoquinolines **6a-c** is believed to be through the formation of the ylidene derivatives[8,9] **8a-c** via elimination of an acetophenone molecule from the diketones **2a-c** with subsequent addition of the aniline derivatives to the formed ylidene followed by cyclization to dihydropyrimido[5,4-c]quinoline intermediate **(A)** which subsequently underwent oxidation in presence of the ylidene derivatives[10] **8a-c** as portrayed in scheme (2).

The structure proof of the pyrimidoquinoline derivatives **6a-c** was further supported by an independent synthesis. This involved, fusion of benzal barbituric acid derivatives **8a-c** with the corresponding aniline derivatives to yield **6a,d,e**. This was confirmed in the case of **6a** by undepressed mixed melting point of the

products obtained by the two methods and identify of their R_f value on TLC (silica gel, pet. ether 40-60/EtOAc, 1:1).



Scheme (2)

However, the pyridopyrimidine derivatives **7a-c** were obtained by treatment of the diketones **2a-c** with ammonium carbonate in acetic acid.

The structure of **7a-c** were established on the basis of their analytical and spectral data. Also, the structure of **7a** was further confirmed through its identical melting point with that reported in literature[11].

On the other hand, fusion of o-phenylenediamine, o-aminothiophenol, or o-aminophenol with 1,3-dimethyl-5-arylidene barbituric acid derivatives **8a,b** in attempts to obtain the corresponding azepines **11a-e** were unsuccessful. Benzimidazole, benzthiazole and benoxazole derivatives **10a-e**, in addition to the corresponding benzyl barbituric acid derivatives **9a,b** were obtained instead of the anticipated azepines **11a-e**.

This reaction was followed by TLC then the products column chromtographed on silica gel using a mixture of petroleum ether 40-60/ EtOAc as elution solvent. TLC showed three spots, the upper one corresponds to the benzalbarbituric acid derivatives **9a,b**, the middle spot corresponds to the benzazoles **10a-e,** whilst, the lower spot is for 1,3-dimethyl barbituric acid.

The structure of benzyl barbituric acid derivatives **9a,b** were confirmed through their identical melting points with those reported in the literature[10,12]. The IR and ^{1}H-NMR spectra of 1,3-dimethyl-5-(p-methoxybenzyl) barbituric acid **9b** showed further evidence of its structure.

Also, the benzazole structures **10a-e** were proved by the identical melting points with those reported in literature[13-15], besides the IR, ^{1}H-NMR, MS spectra. Considering compound **10b,** its IR showed C=C of the aromatic system, whilst its ^{1}H-NMR showed the signals of two aromatic rings, one a 1,4-disubstituted benzene indicated by the AA`BB` system [at δ 8.00 (J = 9Hz) and 7.01 (J=9 Hz)] and the second a 1,2-disubstituted benzene ring represented by the multiplet at δ 7.25 of four aromatic protons. In addition the mass spectrum gave a molecular ion peak as a base peak 224 (m/z). The probable reaction mechanism for formation of benzazoles 10a-e and benzyl barbituric acid derivatives 9a,b is displayed in the following scheme (3).

It is thought that the arylidene **8** serves as oxidizing agent. This behavior was investigated previously by Tanaka and co-workers[10] who have reported the oxidation of thiols to disulphides at the expense of 5-arylidene-1,3-dimethyl barbituric acid derivatives **8** with concomitant formation of their dihydro derivatives **9**.

Again, the reaction of 1,3-dimethyl barbituric acid **(1)** with catechol in the presence of potassium ferricyanide does not give the anticipated benzofuro[2,3-d] pyrimidine **12**[16], but gave the benzofuro adduct **13a** [17]. Its structure was ascertained by elemental analysis, IR, ^{1}H-NMR and Ms.

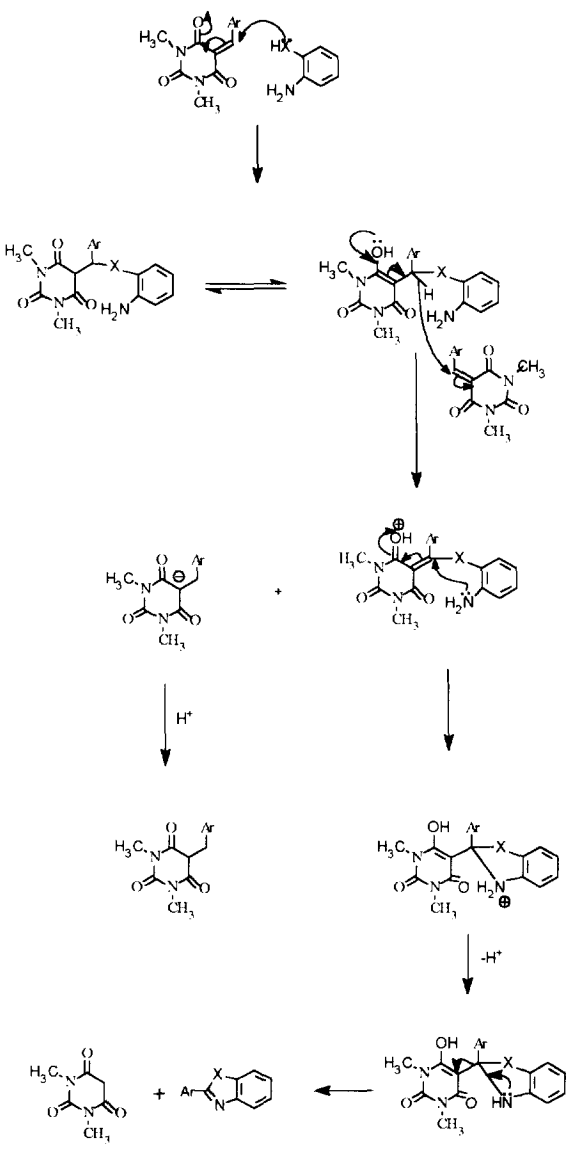
The ^{1}H-NMR spectrum of **13a** showed, in addition to four N-CH_3 singlets (at δ 3.25, 3.42. 3.75 and at 3.35),a doublet and triplet (at δ 4.15, 4.00) due to H-5 and H-6, respectively. Also there is a doublet (at δ 6.9) due to H-7 and one singlet (at δ 7.1) due to H-10. Furthermore, the small coupling of 2 Hz between H-5 and H-6 suggests the *cis*- configuration of these two protons. In addition , its mass spectrum gave a molecular ion peak 418 (m/z).

The formation of the adduct **13a** was probably through the addition[17] of 1,3-dimethyl barbituric acid **(1)** to the diene of the furan ring in compound **12**.

Acetylation of **13a** with acetic anhydride/pyridine mixture afforded the diacetate derivative **13b**. Its IR spectrum showed the carbonyl absorption at 1770 cm^{-1} (-$OCOCH_3$) besides, the absorption at 1685 cm^{-1} (H_3C-N-CO).

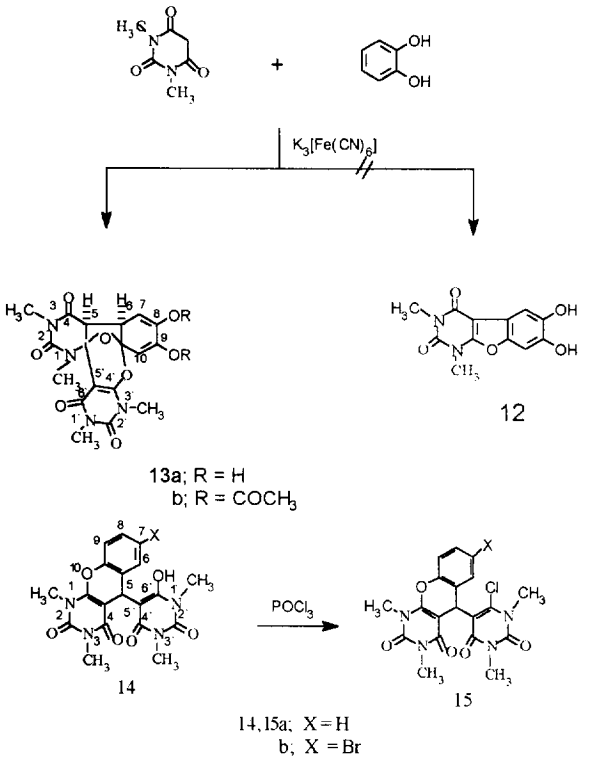
Furthermore, refluxing equimolar ratios from 1,3-dimethyl barbituric acid **(1)** and salicylaldehyde or its bromo derivative in methanol in the presence of hydrochloric acid resulted in cyclo-condensation to give benzopyrano[2,3-d]pyrimidines **14a,b**[18]. Follow up of this reaction by TLC (silica gel, EtOAc/Acetone, 9:1) displayed a complete disappearance of 1,3-dimethyl barbituric acid **(1)** and the presence of a considerable amount of the unreacted salicylaldehyde derivative used. This favours the formation of **14a,b** from 1,3-dimethyl barbituric acid **(1)** and salicylaldehyde derivative in a 2:1 ratio. The structures of **14a,b** was supported by analytical and spectral studies. Their IR spectra showed the presence of C=C, CO, CH_3 and CH functions. The ^{1}H-NMR spectrum of **14a** showed, in addition to four N-CH_3 singlets (at δ 3.02, 3.23, 3.33 and 3.55), a two broad singlets at δ 5.10 and 4.10 due to H-5 and H-5`, respectively. Also, there is a multiplet at δ 7.00-7.40 of four aromatic protons (H-6, H-7, H-8, H-9).

Treatment of **14a,b** with $POCl_3$ produced the corresponding chloroderivatives **15a,b**. The main characteristic features of their IR spectra was the absence of the OH group. Further confirmation of structures **15a,b** was illustrated by the mass fragmentation pattern of **15a** which is consistent with the proposed structure.



(X = N,O, or S)

Scheme (3)



An attempt to obtain the anilino derivative **16a** through fusion of chloroderivative **15a** with p-toluidine failed. Instead, the 5-anilinobenzopyrano [2,3-d] pyrimidine derivative **17** was produced.

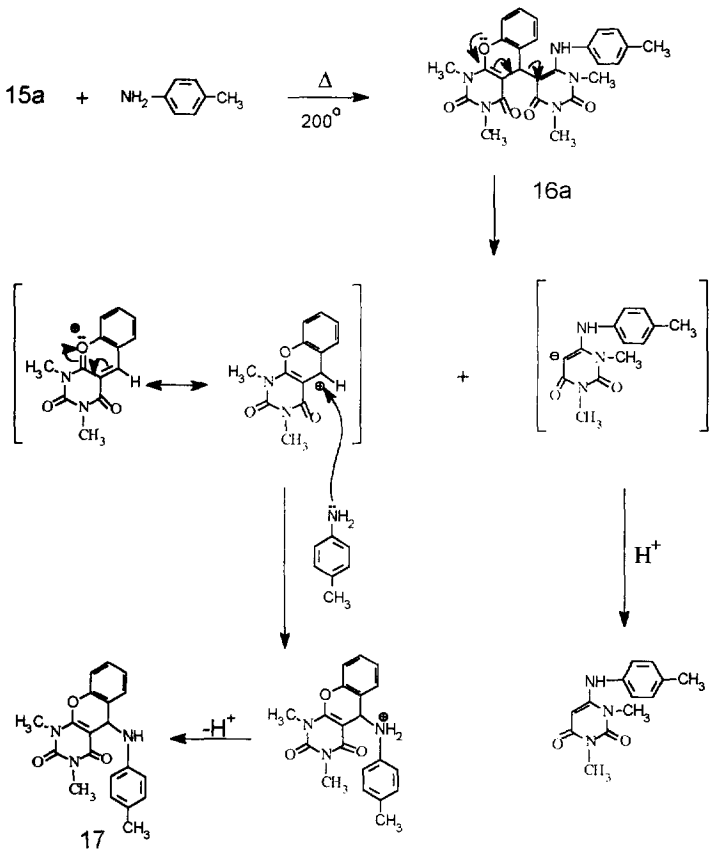
The 5-anilinobenzopyrano[2,3-d]pyrimidine structure for derivative **17** was adopted in view of elemental analysis as well as its IR, ^{1}H-NMR and Ms spectra. Its ^{1}H-NMR spectrum showed only two N-CH3 singlets (at δ3.50 and 3.80). In addition, the mass spectrum of **17** revealed the presence of molecular ion peak at 349, m/z. The loss of 6-(p-toludino)-1,3- dimethyl uracil was in line with that reported by Wawzonek [19].

The plausible pathway for the formation of **17** is depicted in scheme (4).

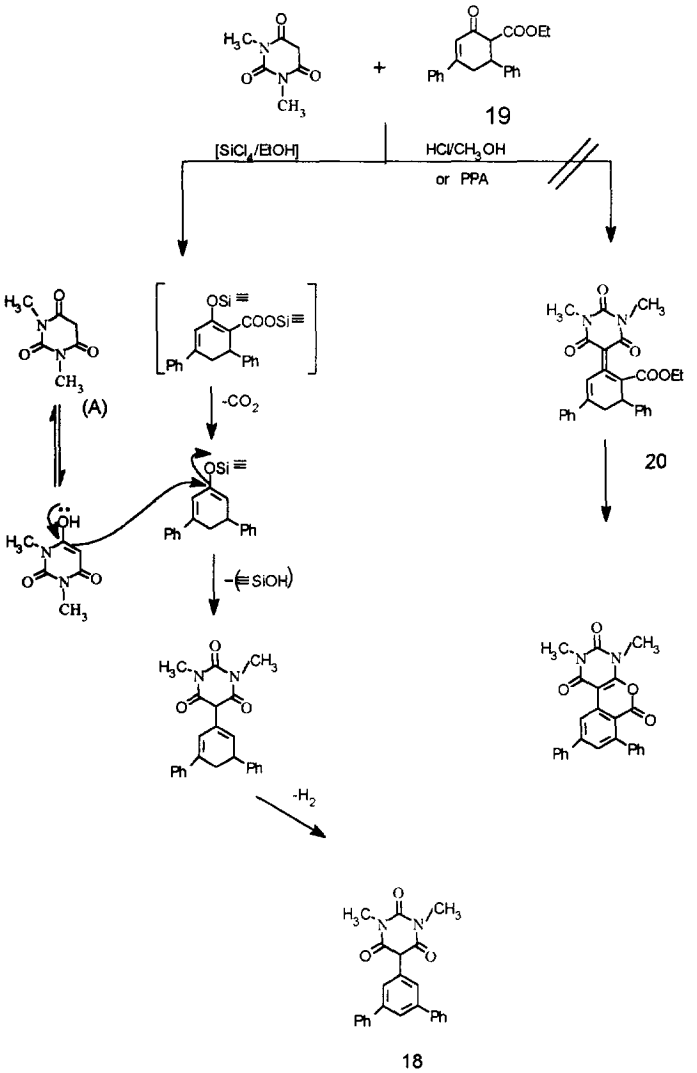
Attempts to obtain the α,β-unsaturated ketone **20** through condensation of 1,3-dimethyl barbituric acid (**1**) with the cyclic β-ketoester **19**[20] in presence of either methanol/hydrochloric acid or polyphosphoric acid were unsuccessful. However, when this reaction was conducted in absolute ethanol and in presence of silicon tetrachloride[21] compound **18** was obtained (Scheme 5).

Structure of **18** was supported by elemental analysis, IR, ^{1}H-NMR and mass spectra. Its IR spectrum showed absorptions at 2950 (CH_3, $CH_{str.}$) 1680, 1741 (CO), 1600 (C=C). The ^{1}H-NMR of **18** showed the presence of 6H (two N-CH_3) and a singlet (3H of 1,3,5-trisubstituted benzene moiety) at δ 7.60, the latter in a ratio of 3 : 10 (with other aromatic protons). Additionally, the Ms fragmentation pattern of compound **18** was in good agreement with the proposed structure. It showed fragments at 229 (m/z) (1,3-diphenylbenzene) and at 155 (m/z) (1,3-dimethyl barbituric acid).

The formation of 5-(3',5'-diphenylphenyl)barbituric acid derivative **18** may be assumed to proceed via formation of the intermediate disilyl derivative of β-keto ester **19** followed by decarboxylation to give the siloxy derivative, which is attacked by 1,3-dimethyl barbituryl anion with subsequent dehydrogenation of the product formed to obtain compound **18** (Scheme 5).



Scheme (4)



Scheme (5)

EXPERIMENTAL

Melting points °C (uncorrected) were taken on a Fisher electric melting point apparatus. Proton NMR spectra were recorded in CDCl3 unless otherwise specified. ^{1}H-NMR spectra were obtained on Varian-Gemini 200 MHz, 270 MHz and Bucker 250 MHz machines. Chemical shifts are reported in ppm (δ) downfield from internal tetramethyl silane. IR spectra were recorded using KBr wafer technique. Mass spectra were recorded on GC-Ms GP-1000 EX. Schiwadzu (Japan) machine.

1,3-Dimethyl-5-(1`-aryl-2`benzoyl ethane) barbituric acids 2a-c:

A solution of **1** (5g, 0.03mol), α,β-unsaturated ketones (0.03mol) and triethyl amine (0.3ml) in methanol (50ml) was refluxed at 80-5°C for 4 hrs. On cooling the reaction mixture, the product was precipitated, filtered off and crystallised from ethanol to give **2a,b**. However, compound **2c** was separated as an oily substance which was purified with column chromatography on silica gel using pet. ether 40-60/EtOAc as eluent. The product solidified after evaporation of most of the eluent, then was left for three days at room temperature.

2a : (76%), mp 150°C (lit.[22] mp 148°C); ^{1}H-NMR δ 3.05 (s,3H), 3.12 (s,3H), 3.53 (dd,J=5.5, 18.5Hz, 1H),3.99 (d, J=4Hz, 1H), 4.09 (dd, J=9, 18.5 Hz, 1H), 4.36 (ddd,J=4, 5.5, 9Hz, 1H) and 7.06-8.10 (m,10H). **2b** : (67%); mp. 139-140°C; IR 1600(C=C), 1650(CO), 1700(CO) cm^{-1}; ^{1}H-NMR δ 3.10 (s,3H), 3.20 (s,3H), 3.50 (dd, 1H), 4.00 (d, 1H), 4.10 (dd, 1H), 4.40 (ddd, 1H) and 7.10-8.00 (m,9H). Anal. Calcd. for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80. Found C, 62.94; H, 5.00. **2C** : (70%); mp 140-1°C, IR 1590(C=C), 1650(CO), 170(CO) cm^{-1}, ^{1}H-NMR δ 3.10 (s,3H), 3.15 (s,3H), 3.50 (dd, 1H), 3.75 (s,3H), 4.0 (d, 1H), 4.05 (dd, 1H), 4.35(ddd, 1H), 6.8-8.05 (m,9H). Anal. Calcd. for $C_{22}H_{22}N_2O_5$ C, 66.99; H, 5.62. Found C, 66.59; H, 5.47.

Pyrimido[5,4-c]quinolines 6a-e:

Method (A):

A solution of the diketone **2a-c** (0.01 mol), aryl amine (0.012 mol) and p-toluene sulphonic acid (20 mg) in xylene (30 ml) was refluxed with a Dean-Stark trap for 8hrs. after which the xylene was evaporated at reduced pressure, the residue was treated with ethanol, the products were separated by filtration, and purified by recrystallization from glacial acetic acid.

Method (B):

A mixture of 1,3-dimethyl barbituric acid arylidene derivative **8a-c** (0.01 mol) and arylamine (0.01 mol) was fused in an oil bath at 150°C for one hour. The reaction mixture was cooled and treated with ethanol. The precipitated products were filtered off and purified by recrystallization from glacial acetic acid as yellow crystals.

6a : (60%), mp > 300°C; ^{1}H-NMR δ 2.40 (s,3H), 3.35 (s,3H), 3.87 (s,3H) 7.10-7.40 (m,5H), 7.55 (brs, 1H), 7.60 (brd, 1H) and 7.92 (d,1H); Ms, m/z (relative intensity) 331(100, M$^+$). Anal. Calcd. for $C_{20}H_{17}N_3O_2$ C, 72.49; H, 5.17; N, 12.68. Found C, 72.09; H, 4.94; N, 12.72. **6b** : (55%); mp > 300°C; ^{1}H-NMR δ 2.40 (s,3H), 3.38 (s,3H), 3.85 (s,3H), 7.10-8.00 (m,7H); Ms, m/z (relative intensity) 366,368(100 and 33, M$^+$, M$^+$+2) . Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.66; H, 4.40. Found C, 66.00; H, 4.10. **6c** : (50%); mp 250°C; Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30. Found C, 69.50; H, 5.20. **6d** : (60%); mp >300°C; Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.29. Found C, 63.80; H, 4.37. **6e** : (48%); mp > 300°C; ^{1}H-NMR δ 3.40 (s,3H), 3.70 (s,3H), 3.87 (s,3H), 6.62-7.90 (m,8H). Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93. Found C, 69.30; H, 4.90.

Pyrido[2,3-d]pyrimidines 7a-c:

To a solution of 1,5-dicarbonyl compound 2a-c (0.005 mol) in acetic acid (25 ml) was added ammonium carbonate (2.5g). The mixture was refluxed for 8hrs. The solvent was evaporated and the residue was treated with dilute ammonium hydroxide (40 ml). The formed precipitate was removed by filtration, washed to neutrality with water and recrystallised from ethanol to give 7a-c.

7a : (68%); mp 248°C (lit.[11] mp 250-2°C). **7b** : (60%); mp 198-200°C; ^{1}H-NMR δ 2.95 (s,3H), 3.40 (s,3H), 7.00-8.23 (m,10H); Ms, m/z (relative intensity) 377,379(15.3, 8.8, M^+, M^++2), 105(100). Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27. Found C, 67.05; H, 4.32. **7c**:(58%); mp 220-1°C; ^{1}H-NMR δ 2.85 (s,3H), 3.45 (s,3H), 3.80 (s,3H), 6.86-8.10 (m,10H). Ms, m/z (relative intensity) 373(18, M^+), 105(100). Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13. Found C, 71.08; H, 4.80.

2-Aryl benzazoles 10a-e and 5-benzyl barbituric acids 9a,b:

A mixture of the 1,3-dimethyl-5-arylidene barbituric acid derivatives **8a,b** (0.01 mol) and aniline derivatives (o-phenylenediamine, o-aminothiophenol or o-aminophenol) was fused in an oil bath at 140°C for one hour. The reaction was followed by TLC which showed three products. They were separated by column chromatography on silica gel using a mixture of pet. ether 40-60/EtOAc as eluent. The first fractions afforded compounds **9** and the second fractions correspond to compounds **10**, while the last fraction was 1,3-dimethyl barbituric acid.

9a : (40%); mp 115°C (lit.[12] mp 116-17°C); IR 1610(C=C), 1700 (CO), 1749(CO) cm^{-1}. **9b** : (37%); mp 90°C (lit. mp 90-2°C); ^{1}H-NMR δ 3.14 (s,6H), 3.41 (d, J=4.5Hz, 2H), 3.74 (t, J=4.5 Hz, 1H), 3.76 (s,3H), 6.75 (AA`BB` system, J=8.5Hz, 2H) and 6.95 (AA`BB` system, J=8.5 Hz, 2H). **10a** : (36%); mp 289°C (lit.[13] mp 285°C); IR 1600 (C=C), 3200(NH) cm^{-1} **10b** : (35%); mp 230°C (lit.[14] mp 227°C); IR 1600 (C=C), 3200(NH) cm^{-1}; ^{1}H-NMR δ 3.82 (s,3H), 7.01 (AA`BB` system, J=9Hz, 2H), 7.25 (m,4H), 7.62 (brs, 1H) and 8.00 (AA`BB` system, J=9Hz, 2H). **10c** : (40%); mp 112°C (lit.[15] mp 114°C); IR 1600 (C=C) cm^{-1}. **10d**: (38%); mp 129-131°C (lit.[15] mp 134°C); IR 1600 (C=C) cm^{-1}; ^{1}H-NMR δ 3.88 (s,3H), 7.00 (AA`BB` system, J=9Hz, 2H), 7.20-7.90 (m,4H) and 8.05 (AA`BB` system, J=9Hz, 2H). **10e** : (37%); mp 102 °C (lit.[15] mp 102-4°C); IR 1600 (C=C) cm^{-1}.

Benzofuro[2,3-d]pyrimidine adduct 13a:

Catechol (0.01 mol) was added to a suspension of 1 (1.56g, 0.03 mol) and sodium acetate (4.08g, 0.03 mol) in aqueous acetone (1:1, 50 ml). To this solution, an aqueous solution of potassium ferricyanide (9.87g, 0.03 mol) containing sodium acetate (4.08g, 0.03 mol) was added dropwise with constant stirring. The precipitate that formed was filtered off, washed several times with water and purified by dissolving it in a sodium hydroxide solution then precipitating by hydrochloric acid to give **13a**, (86%); mp > 300°C; IR 1600 (C=C), 1650(CO), 3300(OH) cm^{-1}; ^{1}H-NMR (DMSO) δ 3.20 (s, 3H), 3.35 (3H under peak of solvent), 3.42 (s,3H), 3.75 (s,3H), 4.10 (t, J=2Hz,1H, H-6), 4.15 (d, J=2Hz, 1H, H-5), 6.90 (d, J=2Hz, 1H, H-7)7.10 (s,1H), 8.50 (brs, 1H, OH) and 9.50 (brs, 1H, OH.); Ms, m/z (relative intensity) 418(1.9, M^+), 416(27.5, M^+-2), 326(100). Anal. Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.68; H, 4.34; N, 13.39. Found C, 51.32; H, 4.50; N, 13.24.

Acetylation of benzofuro[2,3-d] pyrimidine: formation of the diacetate 13b:

Compound **13a** (0.005 mol) was dissolved in acetic anhydride/pyridine mixture (1 : 1, 25 ml). The reaction mixture was left overnight at room temperature and the crushed ice was added to it. The separated solid was filtered off, washed with water and recrystallised from ethanol to give **13b** as colorless crystals, (82%); mp 290°C; IR 1600(C=C), 1650(CO), 1685(CO), 1770(OCOCH$_3$) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_4O_{10}$: C, 52.59; H, 4.41. Found C, 52.24; H, 4.30.

1,3-Dimethyl-5-(1`,3`-dimethyl-2`,4`,6`-trioxo-5`pyrimidinyl)-benzopyrano[2,3-d]pyrimidine-2,4-diones 14a,b:

A solution of 1 (1.56g, 0.01 mol) and the appropriate salicylaldehyde derivative (0.005 mol) in methanol (30 ml) in the presence of hydrochloric acid (2-3 drops) was refluxed for 30-45 min. The reaction mixture was cooled. The solid that separated was filtered off, dried and recrystallised from chloroform/methanol mixture as colorless crystals. **14a** : (83%); mp 238-9°C (lit.[23] mp 237°C); ^{1}H-NMR δ 3.02 (s,3H), 3.23 (s,3H), 3.33 (s,3H), 3.55 (s,3H), 4.10 (brs, 1H), 5.10 (brs, 1H) and 7.00-7.40 (m,4H).**14b** :

(85%); mp 261-3°C; IR 1595(C=C), 1640(CO), 1700(CO) cm^{-1}. Anal. Calcd. for $C_{19}H_{17}BrN_4O_6$: C, 47.81; H, 3.59. Found C, 48.20; H, 3.79.

1,3-Dimethyl-5-(6`-chloro-1`,3`-dimethyl-2`,4`-dioxo-5`pyrimidinyl)-benzopyrano[2,3-d]pyrimidine-2,4-diones 15a,b:

A mixture of benzopyrano[2,3-d]pyrimidine **14a,b** (0.01 mol) and phosphorous oxychloride (40 ml) was heated for one hour. The excess of phosphorous oxychloride was distilled under reduced pressure and the residue was treated with crushed ice then extracted with chloroform (3x100 ml), dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was recrystallised from ethanol to give **15a,b** as buff crystals. **15a** : (72%); mp 279-280°C; Ms, m/z (relative intensity) 416, 418 (69.6 and 27.0, M^+, M^++2), 381(100). Anal. Calcd. for $C_{19}H_{17}ClN_4O_5$: C, 54.75; H, 4.11. Found C, 54.90; H, 4.20. **15b** : (69%); mp 291°C. Anal. Calcd. for $C_{19}H_{16}BrClN_4O_5$: C, 46.03; H, 3.25. Found C, 45.70;H, 3.40.

1,3-Dimethyl-5-(p-toluidino) benzopyrano-[2,3-d]pyrimidine-2,4-dione 17:

A mixture of compound **15a** (2.08g, 0.005 mol) and p-toluidine (0.502g, 0.005 mol) was fused at 200°C in a sand bath for 2hrs. The residue was triturated with ethanol (5ml). The solid that formed was filtered off and recrystallised from ethanol to afford 17 as a grey needles, (65%); mp 297-8°C; IR 1595(C=C), 1660(CO), 1705(CO), 3200-3400(NH); ^{1}H-NMR δ 2.40 (s,1H), 2.54 (s,3H), 3.38 (s,1H), 3.53 (s,3H), 3.84 (s,3H) and 7.00-8.00 (m, 8H); Ms, m/z (relative intensity) 349 (11.3, M^+), 331(100). Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48. Found C, 68.70; H, 5.37.

1,3-Dimethyl-5-(3',5'-diphenylphenyl)barbituric acid 18:

A solution of 1,3-dimethyl barbituric acid (**1**) (0.78g, 0.005 mol), β-keto ester **19**, absolute ethanol (25 ml) and silicon tetrachloride (2.4 ml) was stirred at room temperature for 72hrs. The reaction mixture was poured into ice cold water and the separated product was filtered off and dried. It was dissolved in chloroform (15 ml) and filtered. The chloroform filtrate was evaporated under reduced pressure whereby an oily residue was obtained. It was purified by column chromatography on silica gel using pet. ether 40-60/EtOAc, (3 : 1) to give compound 18, (68%); mp 138-9°C; IR 1606(C=C), 1610(CO), 1741(CO), ^{1}H-NMR δ 3.05 (s, 6H), 3.80 (s, 1H), 7.00-7.58 (m, 10H) and 7.60 (s, 3H) ; Ms, m/z (relative intensity) 385,386 (0.7 and 0.7, M^+, M^++1), 248(100), 229(26.7). Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24. Found C, 75.27; H, 5.45.

REFERENCES

1- Brown D., Jones R., Angyal A. and Grigg G.; J.C.S. Perkin **1**, 1819 (1972).
2- Johnson A.; J. Chem. Soc. **12**, 1626 (1974).
3- Heidelberger C., Arafield F.; J. Cancer Res., **23**, 1226 (1963); C.A. **60**, 2197 (1964).
4- Clerq E.; Anticancer Res. **6**, 549 (1986).
5- Parajapati D., Bhuyan P. and Sandhu J.; J. Chem. Soc. Perkin Trans I, 607 (1988).
6- (a) Lunt E. Comprehensive Organic Chemistry; Barton D., Ollis W., Eds; Pergamon Press: Oxford **4**, 493 (1974). (b) Brown J. Comprehensive Heterocyclic Chemistry; Katritzky A., Rees C., Eds; Pergamon Press. Oxford **3**, 57 (1984).
7- Prajapati D., Sandhu J.; Synthesis, 342 (1988).
8- Kambe S., Saito K., Sakurai A. and Midorikawa H.; Synthesis, 531 (1981).
9- Elmoghayer M., Ibrahim M., Elgandour A. and Elnagdi M.; Synthesis, 635 (1981).
10- (a)Tanaka K., Chen X., Kimura T. and Yoneda F., Chem. Pharm. Bull., **36**(1), 60(1988). (b)Tanaka K., Cken X. and Yoneda F.; Tetrahedron, **44** (11), 3241 (1988).(c) Meissner J., Vander Laan A. and Pandit U.; Tetrahedron Lett., **35**(17), 2757(1994).
11- Troschutz R and Anders E.; Arch Pharm., **325**, 341 (1992).
12- Arthur C., Heyl D., Peck D., Eid C. and Arroyo A.; J Am. Chem. Soc., **63**, 356 (1941).
13- Lchikawa M., Nabeya S., Muraoka K and Hisano T.; Chem. Pharm. Bull. **27** (5), 1255 (1979).

14- **Bacchett T. and Alemagna A.**; AH1. Accad. Nazl. Lincei, Rend Classe Sci. Fis., Mat. Nat., **28, 824** (1960); C.A. **56**, 7304 (1962).
15- **Kalle A. , Ger. Pat.** 1, 137 625 (1962), Appl. 22 (1958); C.A. **59**, 11515 (1963).
16- **Ahluwalia V., Khanduri C. and Kumar R.**; Indian J. Chem., **30** B, 80 (1991).
17- **Tietze L., Woelfling J.** and Schneider G.; Chem. Ber., **124**, 591 (1991).
18- **Ahluwalia V., and Sharma M.**; Indian J.Chem., **30B**, 598 (1991).
19- **Wawzonek S.**; J. Org. Chem., **41** 3149 (1976).
20- **Sammour A., El-Zimaity M. and Abdel-** Maksoud; J.Chem., UAR., **12**, 481 (1969); C. A. **74, 42098** (1971).
21- **Sakurai H.**; Pure & Appl. Chem., **54**, 1 (1982).
22- **Rao A. and Mitra R.**; Indian J. Chem. **12** (10), 1028 (1974).
23- **Akabori S.**; Chem. Ber., **66B**, 139 (1933).

(*Received in UK* 1 *April* 1996; *revised* 3 *June* 1996; *accepted* 6 *June* 1996)