Behaviour of 4-(4-acetoaminophenyl)-4-oxo-but-2-enoic acid towards carbon and nitrogen nucleophiles and use of these products in the synthesis of some interesting heterocycles

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Comportamiento de ácido 4-(4-acetaminofenil)-4-oxo-but-2-enoic ácido frente a nuceófilos de carbono y nitrógeno y uso de estos productos en la síntesis de algunos heterociclos interesantes

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Recibido: 22 de noviembre de 2010; aceptado: 8 de marzo de 2011

RESUMEN

El trabajo presente está dedicado al estudio de la interacción de derivados del ácido β-aroilacrílico (1) con algunos compuestos con metilenos activos en condiciones de reacción de Michael y los aductos de Michael obtenidos (**2a-e**). Cuando el compuesto 1 se hizo reaccionar con cyclohexanone en presencia de acetato de amonio como catalizador, se obtuvo el derivado hidroquinólico (3). La interacción del ácido 1 con hidrocarburos con reactividad alta y moderada, como p. ej. p-xileno y acetanilide en presencia de cloruro de aluminio anhidro en condiciones de Friedel-Craft proporciona (4a-b). Por otro lado, cuándo el ácido 1 se hizo reaccionar con benzylamina en benzene seco se obtuvo ácido 2-benzilamino-4-(4-acetaminofenil)-4-oxobutanoico (5). Este ultimo compuesto se utilizó para sintetizar algunos compuestos heterocíclicos (7-11). También, el aducto aza-Michael (6) se utilizó como el producto de partida clave para la síntesis de algunos compuestos heterocíclicos interesantes, como p. ej. los derivados de piridazinona, oxazinona y furanona (13-16).

Palabras claves: ácido β-aroilacrílico; reacción de Michael; reacción de Friedel-Craft; aza Michael; hidroquinolina.

SUMMARY

The present work is devoted to study the interaction of -aroylacrylic acid derivative **(1)** with some containing active methylene compounds under Michael reaction conditions and afforded the Michael adducts **(2a-e)**. When compound **1** was allowed to react with cyclohexanone in the presence of ammonium acetate as catalyst, it afforded hydroquinoline derivative **(3)**. Interaction of the acid **1** with highly and moderately reactive hydrocarbons e.g. *p*-xylene and acetanilide in the presence of anhydrous aluminum chloride under Friedel-Crafts reaction conditions afforded **(4a-b)**. On the other hand, when the acid **1** was allowed to react with benzyl amine in dry benzene yielded 2-benzylamino-4-(4-acetaminophenyl)-4-oxobutanoic acid **(5)**. This later compound was used to synthesize some heterocyclic compounds **(7-11)**. Also, aza Michael adduct **(6)** used as the key starting material for the synthesis of some interesting heterocyclic compounds e.g. pyridazinone, oxazinone and furanone derivatives (**13-16**).

Key words: β-aroylacrylic acid; Michael reaction; Friedel-Crafts reaction; aza Michael; hydroquinoline.

RESUM

Aquest treball està dedicat a l'estudi de la interacció de derivats de l'àcid β-aroïlacrílic (1) amb alguns productes amb metilens actius en condicions de reacció de Michael i els adductes de Michael obtinguts (2a-i). Quan el producte 1 es va fer reaccionar amb ciclohexanona en presència d'acetat d'amoni com a catalitzador, es va obtenir el derivat hidroquinòlic (3). La interacció de l'àcid 1 amb hidrocarburs amb reactivitat alta i moderada com p. ex. p-xilè i acetanilida en presència de clorur d'alumini anhidre en condicions de Friedel-Craft proporciona (4a-b). D'altra banda, quan l'àcid 1 es va fer reaccionar amb benzilamina en benzè sec, es va obtenir àcid 2-benzilamino-4-(4-acetaminofenil)-4-oxobutanoic (5). Aquest producte es va utilitzar per sintetitzar alguns compostos heterocíclics (7-11). També, l'adducte aza-Michael (6) es va utilitzar com el producte de partida clau per a la síntesi d'alguns compostos heterocíclics interessants, com p. ex. els derivats de

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piridazinona, oxazinona i furanona (13-16).

Paraules claus: àcid β-aroïlacrílic; reacció de Michael; reacció de Friedel-Craft; aza-Michael; hidroquinolina.

INTRODUCTION

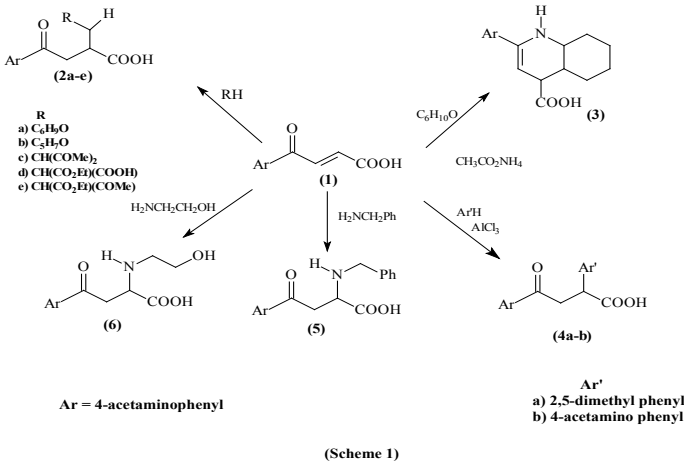
Non acidic or weakly acidic NSAIDs like celecoxib[1] and refecoxib[1] have been developed recently and so have drawn the attention of medicinal chemists as they preferentially act by inhibiting COX-II enzyme and possessed lower incidence of gastric ulcers than the acidic NSAIDs which inhibit COX-I and COX-II enzyme like indomethacid and aspirin. The main trend nowadays in pain therapy focuses on improved nonsteroidal analgesics which are effective as an analgesic but devoid of the side effects which are inherent to traditional NSAIDs.

In terms of this aspect, many studies have been focused on pyridazin-3(*2H*)-ones, which are characterized to process good analgesic and anti-inflammatory activities, besides these studies have indicated that the pyridazinone ring substitutions at the six position, and the presence of acetamide side chain when linked to the lactam nitrogen of pyridazinone ring at the two position improve the analgesic and anti–inflammatory activity along with nil or very low ulcerogenicity [2-7]. In the present investigation the authors aimed to prepare pyridazin-3(*2H*)-one derivative **16** which bear nitrogen moiety at the four positions for the first time and thiocarbamoyl group at position-2 with anticipated NSAIDs activity.

RESULT AND DISCUSSION

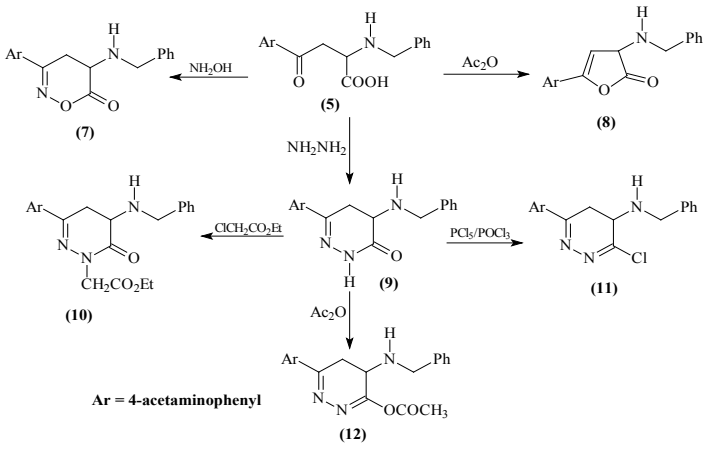
The author aimed through this work to study the behaviour of acid **(1)** towards some containing active methylene compounds (Scheme 1). Thus, the interaction of acid **1** with active methylene compounds namely, cyclohexanone, cyclopentanone, acetylacetone, ethyl cyanoacetate and ethyl acetoacetate in the presence of NaOH (50 %) as catalyst[8, 9] afforded the Michael adducts **(2a-e)**. ^{1}H NMR spectrum of compound **2c** in DMSO showed the following signals (δ ppm) 1.9 (m, 1H C<u>H</u>-COOH), 2.1 (s, 6H, methyl protons), 2.3 (s, 3H, NHCOC<u>H</u>$_3$ methyl proton), 3.5 (d, 2H, methylene protons), 6.7 (s, 1H, NH-D$_2$O exchangeable), 6.9 (d methane proton COC<u>H</u>CO),7.7; 7.8 (2d, 4H, ArH) and 10.5 (s, 1H, OH-D$_2$O exchangeable). For the compound **2d** its IR spectrum devoid any band for ᵘCN because it converted to the corresponding carboxyl group during the reaction. EIMS of compound **2d** exhibits M/e at 363 ($M^{\cdot+}$). Also, EIMS of compound **2e** exhibits M/e at 363 ($M^{\cdot+}$). On the other hand, when compound **1** was allowed to reaction with cyclohexanone in the presence of ammonium acetate as catalyst, it afforded 2-(4-acetaminophenyl)-4-carboxy-5,6,7,8-tetrahydroquinoline **(3),** EIMS exhibits M/e 314 ($M^{\cdot+}$). Interaction of the acid **1** with highly and moderately reactive hydrocarbons e.g. *p*-xylene and acetanilide in the presence of anhydrous aluminum chloride under Friedel-Crafts reaction conditions[10, 11] afforded 2-[2,5-dimethylphenyl/ and/ or 4-acetaminophenyl]-4-(4-acetaminophenyl)-4-oxobutanoic acid (**4a and 4b**), respectively. EIMS of **4a** exhibits m/e 339 ($M^{\cdot+}$).

Recently12 it was reported that 3-(4-bromobenzoyl) acrylic acid underwent aza Michael addition with benzyl amine this prompted us to extend the reaction to include the behaviour of 4-(4-acetaminophenyl)4-oxo-but-2-enoic acid towards benzyl amine to clarify and threw more precise information about the course of the reaction. Thus, when acid **1** was allowed to react with benzyl amine in dry benzene yielded 2-benzylamino-4-(4-acetaminophenyl)-4-oxobutanoic acid **(5)**. EIMS of aza Michael adduct **5** exhibits m/e 340 ($M^{\cdot+}$). ^{1}H NMR spectrum of compound **5** in DMSO (δ ppm) exhibits signals at 2.4 (s, 3H, CH_3CO), 2.7 (octet, 2H methylene protons of acid moiety, non equivalent disteretopic protons), 3.6 (s, 2H methylene protons of benzyl moiety), 4.1 (q, 1H, methane protons), 6.4 (s, 1H, NH exchangeable), 6.6 (s, 1H, NH exchangeable), 7.7-7.9 (m, 9H, ArH) and 12.1 (broad singlet, OH protons exchangeable).



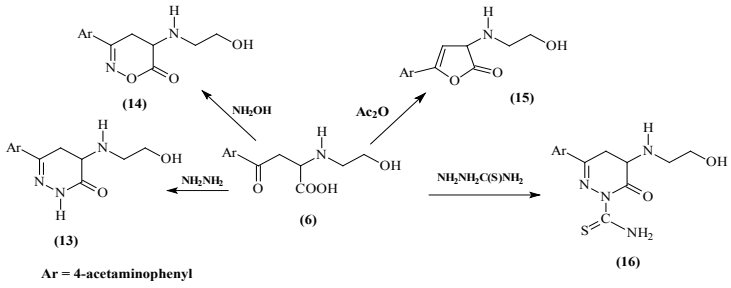
(Scheme 1)

The structure of the compound **5** was inferred chemically from ring closure to give some interesting non-mixed and mixed heterocyclic systems **(7-12)** (Scheme 2). Interaction of the aza Michael adduct product **5** with hydroxylamine hydrochloride in pyridine yielded the oxazinone derivative **(7)**. When the acid **5** was submitted to react with warming acetic anhydride on water bath it yielded 3-benzylamino-5-(4-acetaminophenyl)-2,3-dihydrofuran-2-one **(8)**. Interaction of the compound **5** with hydrazine hydrate in boiling ethanol afforded 4-benzylamino-6-(4-acetaminophenyl)-4,5-dihydro-3(*2H*)-pyridazinone **(9)**. EIMS of compound **9** exhibits m/e =232 ($M^{\cdot+}$-CH_2Ph) which agreed well with the proposed structure. Compound **9** was considered as pre key starting material in which it reacts with carbon electrophiles e.g. ethyl chloroacetate and acetic anhydride and yielded the ethyl ester **(10)** and acetoxy derivative **(12)** and with phosphoryl chloride in the presence of phosphorous pentachloride and yielded the chloropyridazine **(11)**. Thus, interaction of the pyridazinone **9** with ethyl chloroacetate in dry acetone in presence of anhydrous K_2CO_3[13] yielded ethyl [6-(4-acetaminophenyl)-4-(benzylamino)-4,5-dihydro-3(*2H*)-pyridazinone-2-yl]acetate **(10)**, EIMS exhibits m/e = 422 ($M^{\cdot+}$). On the other hand, when compound **9** was allowed to react with acetic anhydride it yielded 6-(4-acetaminophenyl)-3-acetoxy-4-(benzylamino)-4,5-dihydropyridazine (**12**), EIMS exhibits m/e = 378 ($M^{\cdot+}$).



(Scheme 2)

When compound **1** was submitted to react with ethanolamine in boiling ethanol it afforded 4-(4-acetaminophenyl)-2-(2-hydroxyethylamino)-4-oxobutanoic acid **(6)**, EIMS showed m/e = 293 ($M^{\cdot+}$) which agreed well with the proposed structure. The reaction takes place via nucleophilic addition by the lone pair of nitrogen on α,β-unsaturated ketone moiety and yielded the aza Michael adduct **(6)**. The aza Michael adduct **6** use as a key starting material in synthesis of some interesting heterocyclic compounds e.g. pyridazinones, oxazinones and furanones derivatives (Scheme 3). Thus, when compound **6** was allowed to react with hydrazine hydrate in boiling ethanol and yielded 6-(4-acetaminophenyl)-4-(2-hydroxyethylamino)-4,5-dihydropyridazin-3(*2H*)-one **(13)**. The reaction takes place via nucleophilic addition to the carbonyl moiety followed by ring closure. On the other hand, the acid **6** reacts with hydroxylamine hydrochloride in boiling pyridine and yielded the oxazinone derivative **(14)**. The reaction takes place via nucleophilic attack of the lone pair of nitrogen on the carbonyl moiety followed by the ring closure to give the desired product. Dehydration of compound **6** by using acetic anhydride afforded 5-(4-acetaminophenyl)-3-(2-hydroxyethanolamino)-furan-2(*3H*)-one**(15)**. 1,4-azaalkylation of 3-(4-acetoamino)benzoylprop-2-enoic acid with ethanolamine **(6)** was submitted to react with thiosemicarbazide in boiling pyridine afforded 6-(4-acetaminophenyl)-4-(2-hydroxyethylamino)-4,5-dihydro-2-thiocarbamoyl-3(*2H*) pyridazinone **(16)**. The reaction takes place via nucleophilic addition to carbonyl moiety followed by ring closure to give the desired product.



(Scheme 3)

EXPERIMENTAL

All melting points are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. Microanalyses were carried out by the Micro Analytical Center at Cairo University. The IR spectra were recorded on FT/IR-300E Jasco spectrophotometer as (KBr) discs. The ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz instrument with chemical shifts (d) expressed in ppm downfield from TMS. Mass spectra were recorded on Shomadzu GC-MS (QP-1000EX) instrument operating at 70eV. The homogeneity of all compounds synthesized was checked by TLC.

4-(4-acetaminophenyl)-4-oxobut-2-enoic acid (1)
A ground mixture of 50 gm acetanilide and 38 gm of maleic anhydride were added to a cooled mixture of 200 ml of carbon disulphide and 185 gm Aluminum chloride in one portion. The temperature of the reaction mixture will be raise to 35°C and the reaction mixture become deep yellow. An additional 100 ml of carbon disulphide was added and the reaction mixture was left at room temperature for 48 hours. At the end of the time the reaction mixture poured onto ice- HCl mixture. The resulting yellow suspension was filtered and crystallized from aqueous alcohol, m.p. 251°C. Elemental analysis for $C_{12}H_{11}NO_4$ (333.23): Calcd: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.9; H, 4.84; N, 6.12.

Reaction of 1 with carbon nucleophiles under Michael reaction conditions:

General procedure:
To a solution of the acid ***(1)*** (0.01 mole), and active methylene compounds namely, cyclohexanone, cyclopentanone, acetylacetone, ethyl cyanoacetate and ethyl acetoacetate (0.02 mole) in absolute ethanol (30 ml), 6 ml of 50 % aqueous sodium hydroxide was added at 40°C. The reaction mixture was left at room temperature for 7 days. The reaction mixture was extract with ether to get rid of any unreacted organic material. The cooled aqueous layer was acidified and extracted with ether. The residual oil after evaporation of the ether was triturated with light petrol (b. p. 40-60°C). The solid obtained was crystallized from the proper solvent.

4-(4-acetaminophenyl)-2-(2-oxocyclohexyl)-4-oxobutanoic acid (2a) was crystallized from EtOH as white crystals; m.p. 200°C. Elemental analysis for $C_{18}H_{21}NO_5$ (331.36): Calcd: C, 65.24; H, 6.39; N, 4.23. Found: C, 66.14; H, 6.81; N, 4.10. IR (KBr) υ_{max} (cm^{-1}): 1677; 1700; 1737 (C=O), 2861 (C-H), 2936 (OH).

4-(4-acetaminophenyl)-2-(2-oxocyclopentyl)-4-oxobutanoic acid (2b) was crystallized from benzene as white crystals; m.p. 185°C. Elemental analysis for $C_{17}H_{19}NO_5$ (317.34): Calcd: C, 64.34; H, 6.03; N, 4.41. Found: C, 65.30; H, 6.41; N, 4.40. IR (KBr) υ_{max} (cm^{-1}): 1680; 1700; 1727 (C=O), 2860; 2955 (C-H), 3150; 3350 (OH).

4-(4-acetaminophenyl)-2-diacetylmethyl-4-oxobutanoic acid (2c) was crystallized from EtOH as white crystals; m.p. 210°C. Elemental analysis for $C_{17}H_{19}NO_6$ (333.34): Calcd: C, 61.25; H, 5.75; N, 4.2. Found: C, 61.44; H, 5.81; N, 4.4. IR (KBr) υ_{max} (cm^{-1}): 1680; 1700; 1744 (C=O), 2849; 2924 (C-H), 3160 (NH), 3341 (OH). ^{1}H NMR (DMSO) δ

(ppm): 1.9 (m, 1H, CH-COOH), 2.1 (s, 6H, methyl protons), 2.3 (s, 3H, $NHCOCH_3$ methyl proton), 3.5 (d, 2H, methylene protons), 6.7 (s, 1H, NH-D_2O exchangeable), 6.9 (d, methane proton, COCHCO) , 7.7, 7.8 (2d, 4H, ArH) and 10.5 (s, 1H, OH-D_2O exchangeable).

5-(4-acetaminophenyl)-3-carboxy-2-(2-ethoxycarbonyl)-5-oxopentanoic acid (2d) was crystallized from benzene as white crystals; m.p. 220°C. Elemental analysis for $C_{17}H_{19}NO_8$ (365.36): Calcd: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.94; H, 5.38; N, 3.89. IR (KBr) υ_{max} (cm^{-1}): 1687; 1700 (C=O), 2919 (C-H), 3170 (NH), 3330 (OH). EIMS, m/e: 365 ($M^{\cdot+}$).

Ethyl[5-(4-acetaminophenyl)-2-aceto-3-carboxy)]-5-oxopentanoate (2e) was crystallized from EtOH as white crystals; m.p. 195°C. Elemental analysis for $C_{18}H_{21}NO_7$ (363.36): Calcd: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.8; H, 5.90; N, 3.89. IR (KBr) υ_{max} (cm^{-1}): 1675; 1700; 1735 (C=O), 3189 (NH), 3300 (OH). EIMS, m/e: 363 ($M^{\cdot+}$).

2-(4-acetaminophenyl)-4-carboxy-5,6,7,8-tetrahydroquinoline (3)

A solution of cyclohexanone (0.01 mole), in absolute ethanol (30 ml) containing excess ammonium acetate, β-aroylacrylic acid **1** (0.01 mole) was added and the reaction mixture was heated under reflux for 3-5 hour. The solid material which separated during reflux was collected by filtration and crystallized from EtOH as pale yellow crystals; m.p. >300°C. Elemental analysis for $C_{18}H_{22}N_2O_3$ (314.38): Calcd: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.80; H, 6.99; N, 8.99. IR (KBr) υ_{max} (cm^{-1}): 1640; 1673 (C=O), 2859; 2933 (CH), 3100 (NH), 3250 (OH). EIMS, m/e: 314 ($M^{\cdot+}$).

2-[2,5-dimethylphenyl/ and/ or 4-acetaminophenyl]-4-(4-acetaminophenyl)-4-oxobutanoic acid (4a and 4b)

Method A:

A solution of the β-aroylacrylic acid **1** (0.01 mole), the aromatic hydrocarbon *p*-xylene and/ or acetanilide (50 ml or 0.01 mole) in carbon disulphide was saturated with dry hydrogen chloride then (0.04 mole) of aluminum chloride was added. A vigorous evolution of hydrogen chloride took place and a yellow paste precipitated. The temperature of the reaction mixture was maintained at 20-25°C. Stirring was continued for an additional 15 hours at room temperature. The reaction mixture was added to HCl–ice mixture. The organic materials were extracted by ether. The etherial solution washed by 10% aqueous sodium carbonate solution. The alkaline solution was acidified by cold diluted hydrochloric acid. The product were crystallized from the suitable solvent to give the corresponding α-aryl-β-aroyl propionic acids derivatives

Method B:

A solution of β-aroylacrylic acid **1** (0.01 mole) and the aromatic hydrocarbon was treated with anhydrous aluminum chloride (0.04 mole). The mixture was heated on the water bath for 10 hours. The mixture was treated as described above

4-(4-acetaminophenyl)-2-(2,5-dimethylphenyl)-4-oxobutanoic acid (4a) was crystallized from EtOH as white crystals; m.p. 280°C. Elemental analysis for $C_{20}H_{21}NO_4$ (339.39): Calcd: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.94; H, 6.64; N, 4.34. IR (KBr) υ_{max} (cm^{-1}): 1635; 1664; 1695 (C=O), 2919 (CH), 3115 (NH), 3325 (OH). EIMS, m/e: 339, 0.5 ($M^{\cdot+}$).

2,4-bis(4-acetaminophenyl)-4-oxobutanoic acid (4b) was crystallized from EtOH as white crystals; m.p. 220°C. Elemental analysis for $C_{20}H_{20}N_2O_5$ (368.38): Calcd: C, 65.21; H, 5.47; N, 7.60. Found: C, 64.21; H, 5.74; N, 7.94. IR (KBr) υ_{max} (cm^{-1}): 1630; 1670; 1692 (C=O), 2990;3100 (CH), 3150 (NH), 3350 (OH).

4-(4-acetaminophenyl)-2-benzylamino-4-oxobutanoic acid (5)

A mixture of β-aroylacrylic acid **1** (0.01 mole) and benzyl amine (0.01 mole) in dry benzene was treated with few drops of piperidine and leave four days at room temperature. The solid that was separated out, filtered off, washed by light petroleum (b.p. 40-60°C), dried and then crystallized from petroleum ether as white crystals; m.p. 160°C. Elemental analysis for $C_{19}H_{20}N_2O_4$ (340.38): Calcd: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.99; H, 5.99; N, 8.54. IR (KBr) υ_{max} (cm^{-1}): 1650; 1686; 1700 (C=O), 2859, 3176 (NH), 3252; 3300 (OH). EIMS, m/e: 340 ($M^{\cdot+}$). ^1H NMR (DMSO) (d ppm): 2.4 (s, 3H, CH_3CO), 2.7 (octet, 2H methylene protons of acid moiety), 3.6 (s, 2H methylene protons of benzyl moiety), 4.1 (q, 1H, methane protons), 6.4 (s, 1H, NH exchangeable), 6.6 (s, 1H, NH exchangeable), 7.7-7.9 (m, 9H, ArH) and 12.1 (broad singlet, OH protons exchangeable).

4-(4-acetaminophenyl)-2-(2-hydroxyethylamino)-4-oxobutanoic acid (6)

A mixture of β-aroylacrylic acid **1** (0.01 mole) and ethanol amine (0.01 mole) was treated with few drops of piperidine in dry benzene and leave four days at r.t. The solid that was separated out was filtered off, washed by light petroleum (b.p. 40-60 °C), dried and then crystallized from EtOH as white crystals; m.p. 155°C. Elemental analysis for $C_{14}H_{18}N_2O_5$ (294.30): Calcd: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.24; H, 6.21; N, 9.64. IR (KBr) υ_{max} (cm^{-1}): 1677 (C=O), 2929 (CH), 3264 (NH), 3305 (OH). EIMS exhibits m/e = 293 ($M^{\cdot+}$).

3-(4-acetaminophenyl)-5-(benzylamino)-4,5-dihydro-6H-1,2-oxazin-6-one (7)

A mixture of aza Michael adduct product **5** in pyridine (20 ml), hydroxylamine hydrochloride (0.01 mole), and water (one ml) was refluxed for 6 hour .The cool mixture was poured into ice-cold diluted hydrochloric acid mixture. The solid separated was crystallized from EtOH as white crystals; m.p. >300°C. Elemental analysis for $C_{19}H_{19}N_3O_3$ (337.37): Calcd: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.57; H, 5.62; N, 12.64. IR (KBr) υ_{max} (cm^{-1}): 1653; 1730 (C=O), 2926 (CH), 3110; 3341 (NH).

5-(4-acetaminophenyl)-3-(benzylamino)-furan-2(3H)-one (8)

A solution of acid **5** (0.01 mole), Michael adducts, and acetic anhydride (20 ml) was heated under reflux for 40 hour. The mixture was concentrated and cooled the colorless solid separated was crystallized from EtOH as white crystals; m.p. 190°C. Elemental analysis for $C_{19}H_{18}N_2O_3$ (322.36): Calcd: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.84; H, 5.62; N, 8.64. IR (KBr) υ_{max} (cm^{-1}): 1673; 1778 (C=O), 3050; 3259 (NH). EIMS exhibits m/e = 323 ($M^{\cdot+}$).

6-(4-acetaminophenyl)-4-(benzylamino)-4,5-dihydro-pyridazin-3(2H)-one (9)

A mixture of 2-acetaminobenzoylacrylic acid **5** (0.01 mole) and hydrazine hydrate (0.01 mole) was heated under reflux in absolute ethanol (30 ml) for 3 hr. The reaction mixture was concentrated. The solid was separated out, filtered off, dried and crystallized from EtOH as white crystals; m.p. 210ºC. Elemental analysis for $C_{19}H_{20}N_4O_2$ (336.39): Calcd: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.94; H, 6.13; N, 16.76. IR (KBr) υ_{max} (cm^{-1}): 1610 (CN), 1662 (C=O), 2896 (CH), 3038; 3289 (OH). EIMS, m/e: 232 ($M^{\cdot+}$-CH_2Ph).

Ethyl[6-(4-acetaminophenyl)-4-(benzylamino)-4,5-dihydro-3(2H)-pyridazinone-2-yl]acetate (10)

A mixture of pyridazinone **9** (0.01 mole), ethylchloroacetate (0.02 mole) and anhydrous K_2CO_3 (0.04 mole) in dry acetone (50 ml) was heated under reflux on water bath for 24 hr. Solvent excess was removed by evaporation and the reaction mixture was diluted with water. The solid that separated was filtered off, dried and crystallized from EtOH as white crystals; m.p. 125ºC. Elemental analysis for $C_{23}H_{26}N_4O_4$ (422.49): Calcd: C, 65.39; H, 6.20; N, 13.26. Found: C, 65.53; H, 6.41; N, 13.52. IR (KBr) υ_{max} (cm^{-1}): 1660; 1744 (C=O), 2928; 2979 (CH), 3123; 3315 (NH). EIMS, m/e: 422 ($M^{\cdot+}$).

6-(4-acetaminophenyl)-4-(benzylamino)-3-chloro-4,5-dihydropyridazine (11)

A mixture of pyridazinone **9** (0.01 mole), $POCl_3$ (0.05 mole) and PCl_5 (0.03 mole) was heated on a water bath for 2 hr. The reaction mixture was poured slowly onto crushed ice. The solid that separated was filtered off and crystallized from EtOH as pale yellow crystals; m.p. 180ºC. Elemental analysis for $C_{19}H_{19}ClN_4O$ (354.83): Calcd: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.57; H, 5.62; N, 15.94. IR (KBr) υ_{max} (cm^{-1}): 1652 (C=O), 3189; 3262 (NH).

6-(4-acetaminophenyl)-3-acetoxy-4-benzylamino-4,5-dihydropyridazine (12) .

A mixture of pyridazinone **9** (0.01 mole) and (20 ml) acetic anhydride was refluxed for one hour on water bath, the reaction mixture was poured onto water and left overnight. The solid separated was filtered off, dried and crystallized from EtOH as pale yellow crystals; m.p. 210ºC. Elemental analysis for $C_{21}H_{22}N_4O_3$ (378.43): Calcd: C, 66.65; H, 5.86; N, 14.8. Found: C, 66.84; H, 5.94; N, 14.98. IR (KBr) υ_{max} (cm^{-1}): 1636; 1664 (CN), 1695; 1726 (C=O), 3190; 3338 (NH). EIMS, m/e: 378 ($M^{\cdot+}$).

6-(4-acetaminophenyl)-4-(2-hydroxyethylamino)-4,5-dihydropyridazin-3(2H)-one (13)

A mixture of acid **6** (0.01 mole) and hydrazine hydrate (0.01 mole) was heated under reflux in absolute ethanol (30 ml) for 3 hr. The reaction mixture was concentrated. The solid was separated out, filtered off, dried and crystallized from EtOH as white crystals; m.p. 185ºC. Elemental analysis for $C_{14}H_{18}N_4O_3$ (290.32): Calcd: C, 57.92; H, 6.25; N, 19.30. Found: C, 57.84; H, 6.72; N, 19.64. IR (KBr) υ_{max} (cm^{-1}): 1680; 1664; 1734 (C=O), 3110 (NH), 3318 (NH and/ or OH).

3-(4-acetaminophenyl)-5-(2-hydroxyethylamino)-4,5-dihydro-6H-1,2-oxazin-6-one (14)

A mixture of acid **6** in pyridine (20 ml), hydroxylamine hydrochloride (0.01 mole), and water (one ml) was refluxed for 6 hour. The cooled mixture was poured into ice-cold diluted hydrochloric acid. The solid separated was crystallized from EtOH as pale yellow crystals; m.p. 160ºC. Elemental analysis for $C_{14}H_{17}N_3O_4$ (291.30): Calcd: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.24; H, 5.72; N, 14.64. IR (KBr) υ_{max} (cm^{-1}): 1670 (C=O), 2960 (CH), 3377 (NH and/ or OH).

5-(4-acetaminophenyl)-3-(2-hydroxyethanolamino)-furan-2(3H)-one (15)

A solution of acid **6** (0.01 mole) of the Michael adducts and acetic anhydride (20 ml) was heated under reflux for 40 hour. The mixture was concentrated and cooled the colorless solid separated was crystallized EtOH as white crystals; m.p. 210ºC. Elemental analysis for $C_{14}H_{16}N_2O_4$ (276.29): Calcd: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.90; H, 5.72; N, 10.26. IR (KBr) υ_{max} (cm^{-1}): 1730 (C=O), 2922 (CH), 3329 (NH and/ or OH), 3377 (OH).

6-(4-acetaminophenyl)-4-(2-hydroxyethylamino)-4,5-dihdro-2-thiocarbamoyl-3(2H)-pyridazinone (16)

A solution of the acid **6** (0.01 mole) in ethanol, thiosemicarbazide and 2 drops of piperidine was refluxed for 10 hour. After cooling the reaction mixture poured into water, the precipitate formed was filtered off washed with water, dried and crystallized from benzene as pale yellow crystals; m.p. 280ºC. Elemental analysis for $C_{15}H_{19}N_5O_3S$ (349.40): Calcd: C, 51.56; H, 5.48; N, 20.04. Found: C, 51.61; H, 5.72; N, 20.26. IR (KBr) υ_{max} (cm^{-1}): 1680; 1671; 1705 (C=O), 2926 (CH), 3331 (NH and/ or OH).

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