Synthesis and Reactions of 4, 6-Diaryl-2,3,4,5-Tetrahydropyridazin-3-ones

M.A.SAYED, A.A.EL-KHAMRY, A.Y.SOLIMAN,
A.A.AFIFY AND E.A.KASSAB
Chemistry Department, Faculty of Science,
Ain Shams University, Abbassia,
Cairo, Egypt

Summary: The hitherto unknown 4,6-diaryl-2,3,4,5-tetrahydro-pyridazin-3-ones (II)a-e were synthesised from the α-aryl, β-aroylpropionic acids (I)a-e either by their reaction with hydrazine hydrate or by their conversion to α,γ-diaryl-$\Delta^{\beta,\gamma}$ butenolides(XI), and treatment of the latter with hydrazine hydrate. (II) afforded 3-chloropyridazine derivative (IV) on its reaction with $POCl_3$, PCl_5.

The 3-chloropyridazine was treated either with sodium azide producing the tetrazolopyridazine derivative (V) or with acylhydrazines to give the triazolopyridazine derivatives (VI)a-c. 3-Acylpyridazines (VII)a & b were obtained on treatment of (II) with acetyl chloride. (II)a was converted to its corresponding thione (VIII), also reacted with benzylamine giving 3-N-benzylpyridazine (IX). (II)a was dehydrogenated to the corresponding dihydropyridazinone (X).

The present work aims to study the behaviour of aroyl acrylic acids, either as α,β-unsaturated acids or α,β-unsaturated ketones, and also to study the effect of two bulky substituents on the activity of the pyridazinone nucleus.

The wide range of pharmacological properties of pyridazinone derivatives such as; modification the heart rate [1], cardiotonic activity [2], anti-hypertensive activity [3,4], and their action on the central nervous system [5,6] and also their use as agricultural fungicides [7] made them worthy to be synthesised.

The β-aroylacrylic acids (I)a-c add m-xylene, p-cymene, p-xylene and/or o-xylene to give the corresponding o-aryl-3-aroyl propionic acids (I)a-e.

The structure of compounds (I)a-e was confirmed by microanalyses and I.R. spectral data (Table-1).

(I)
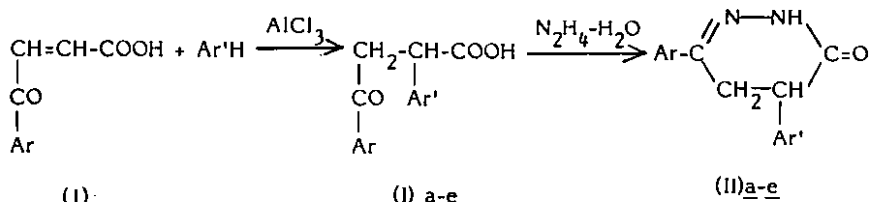
a, Ar=2,4-$(CH_3)_2C_6H_3$-

b, Ar=3,4-$(CH_3)C_6H_3$-

c, Ar=4,2-$Br(CH_3)C_6H_3$-

(I) a-e

a, Ar=Ar'=2,4-$(CH_3)_2C_6H_3$-

b, Ar=3,4-$(CH_3)_2C_6H_3$; Ar'=2,5-$CH_3[CH(CH_3)_2]C_6H_3$-

c, Ar=2,4-$Br(CH_3)C_6H_3$-; Ar'=2,4-$(CH_3)_2C_6H_3$-

d, Ar=2,4-$Br(CH_3)C_6H_3$-; Ar'=2,5-$(CH_3)_2C_6H_3$
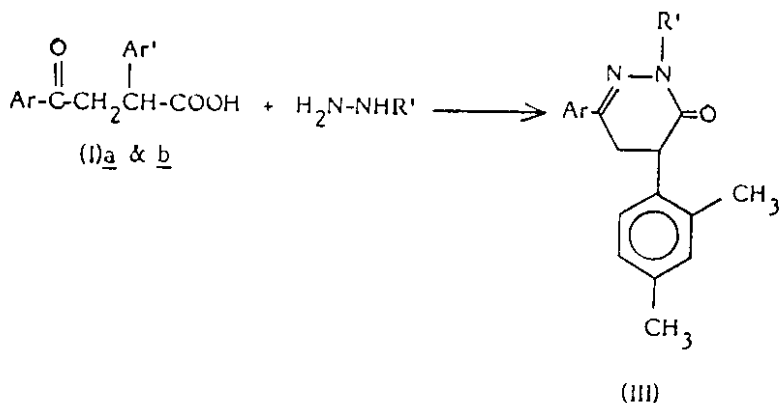
e, Ar=2,4-$Br(CH_3)C_6H_3$-; Ar'=3,4-$(CH_3)_2C_6H_3$-

The reaction of α-aryl-β-aroyl propionic acids (I)a-e with hydrazine hydrate in boiling ethanol gave 4,6-diaryl-2,3,4,5-tetrahydropyridazin-3-ones (II)a-e.

The I.R. spectra of (II)a-e showed strong absorption bands at ν1660-1675 cm^{-1} attributable to CO(cyclic amide), and at ν 3220-3240 cm^{-1} attributable to NH (Table-1).

The PMR spectrum of (II)a (CDCl$_3$) showed signals at δ2.25 (s, 12H of Ar-CH$_3$), δ2.7-2.9 (t, 2H of non-equivalent cyclic CH$_2$), δ 3.8-4.1 (q, 1H of cyclic CH), δ 7.1-7.2 (d, 6H of Ar-H), and 8.1 (broad, 1H of NH).

Also condensation of propionic acids (I) a & e with N-substituted hydrazines namely, phenylphydrazine; 2,4-dinitrophenylhydrazine; semicarbazide and/or salicyloyl hydrazine in boiling ethanol gave 2N-(substituted)-4,
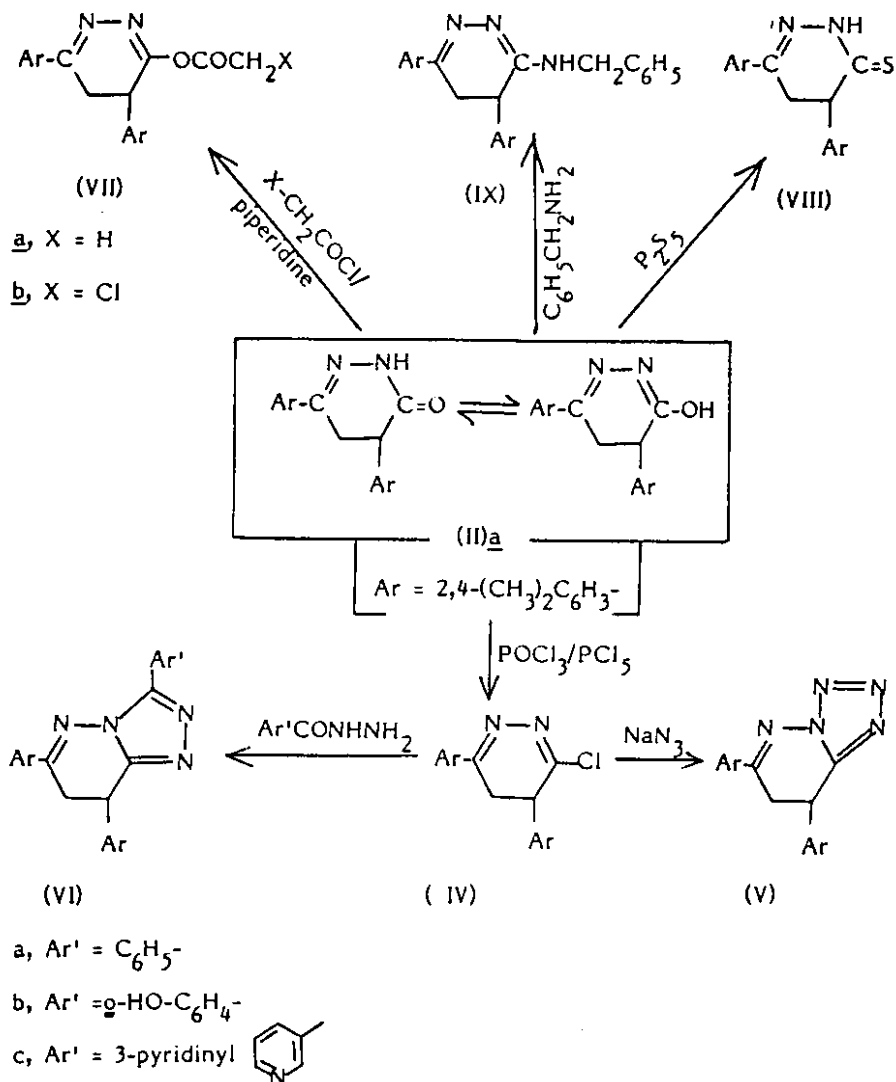
6-diaryl-2,3,4,5-tetrahydropyridazin-3-ones (III)a-e.

The I.R. spectra of (III) showed the presence of CO of cyclic amide at ν 1660-1680 cm^{-1} and absence of NH (Table-1).

As a point of interest [8,9], the presence of pyridazinones (II)a-e in lactam $\rightleftharpoons$ lactim tautomeric equilibrium has been investigated. Thus, the pyridazinone (II)a reacts with POCl$_3$ on steam bath to give the chloro-pyridazine derivative (IV). This confirm the presence of the lactim structure.

The structure of (IV) was supported by its. I.R. spectrum which showed absorption band at ν1640 cm^{-1} attributable to C=N (Table-1).

Treatment of chloropyridazine (IV) with sodium azide afforded tetrazolopyridazine (V).

2,3,4,5-tetrahydropyridazin-3-ones (III)a-e.

(III)

a, Ar=2,4-(CH$_3$)$_2$C$_6$H$_3$-; R'=C$_6$H$_5$-

b, Ar=4,2-Br(CH$_3$)C$_6$H$_3$-; R'=C$_6$H$_5$

c, Ar=2,4-(CH$_3$)$_2$C$_6$H$_3$-; R'=2,4-(NO$_2$)$_2$C$_6$H$_3$-

d, Ar=2,4-(CH$_3$)$_2$C$_6$H$_3$-; R'=CONH$_2$

e, Ar=2,4-(CH$_3$)$_2$C$_6$H$_3$-; R'=2-(OH)C$_6$H$_3$CO-

The reaction scheme shows the following structures and transformations:

(VII)
a, X = H
b, X = Cl

(IX)

(VIII)

X-CH₂COCl/piperidine

C₆H₅CH₂NH₂

P₂S₅

(II)a

Ar = 2,4-(CH₃)₂C₆H₃-

POCl₃/PCl₅

Ar'CONHNH₂

(VI)

(IV)

NaN₃

(V)

a, Ar' = C₆H₅-

b, Ar' = o-HO-C₆H₄-

c, Ar' = 3-pyridinyl

The I.R. spectrum [10] of (V) showed absorption bands at ∿1040–1080 cm^{-1} characteristic of the tetrazole ring and at ν 1615 cm^{-1} attributable to C=N.

Chloropyridazine (IV) reacts with acylhydrazines namely, benzoyl-hydrazine, nicotinoylhydrazine and/or salicyloylhydrazine in boiling n–butanol to give triazolopyridazine (VI) a-c.

The I.R. spectra of (VI) a-c showed absorption band at ν 1620–1630 cm^{-1} attributable to C=N and an additional broad band at ν 3340 cm^{-1} attributable to OH for compound (VI) b.

The behaviour of pyridazinones (II) as lactam   lactim tautomeric equilibrium has also been investigated by reaction of (II)a with acetyl chloride and/or chloroacetyl chloride in the presence of few drops of piperidine to give the corresponding 3-acylpyridazines (VII)a, b.

The I.R. spectra of (VII) a & b showed absorption bands characteristic for CO of esters, ν (1725 & 1730 cm^{-1}),

C=N at ν1610 & 1605 cm^{-1} respectively, and absence of any bands characteristic of NH.

On the other hand, the pyridazinone (II)a reacts with phosphorus pentasulphide [9] in boiling xylene to give the corresponding pyridazine-3-thione (VIII) in which thionation together with dehydrogenation takes place. This proves the presence of the lactam structure in pyridazinones (II).

The I.R. spectrum of (VIII) showed absorption bands at ν 1607 cm^{-1} due to C=N and at ν 1545 cm^{-1} due to C=S. Fusion of (II) a with excess of benzylamine gave 3-N-benzylpyridazine (IX). The I.R. spectrum of (IX) showed absorption band at ν1595 cm^{-1} (C=C and C=N).

Recently, it has been reported [9] that tetrahydropyridazinones (II) underwent dehydrogenation upon treatment with bromine and acetic acid in a similar manner observed in the bromination of pyrazolines [11]. Therefore the reaction of the pyridazinones (II) a, c & e with bromine and acetic acid afforded dihydropyridazinones (X) a-c.

The I.R. spectra of (X) showed absorption bands at ν 1650-1680 cm^{-1} (CO of cyclic amide) and at ν 3290 cm^{-1} (NH). The PMR spectrum of (X)a showed signals at δ 2.25 (12H of Ar-CH$_3$) and signals at δ 7.0-7.4 (6H of aromatic rings and 1H of olefinic double bond).

α-Aryl-β-aroyl-propionic acid (I)a was easily dehydrated by boiling with acetic anhydride yielded α, β-diaryl--butenolide (XI), beside 2-acetoxy-3, 5-(2',4'-dimethyl)-diphenyl furan (XII).

The I.R. spectrum of (XI) showed strong absorption band at ν1760 cm^{-1} characteristic of five-membered lactone and a band at ν1610 cm^{-1} for conjugated C=C. On treatment of (XI) with hydrazine hydrate (II)a was produced in quantitative yield. The I.R. spectrum of (XII) showed absorption bands at ν 1740 cm^{-1} (attributable to CO of ester) and at ν1610 cm^{-1} (C=C). The structure of (XII) was confirmed by the following chemical proofs:- i) It can be prepared by boiling the co-product (XI) with acetic anhydride. ii)

(II)

(X)
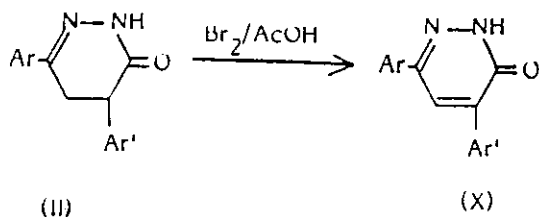
a, Ar=Ar'=2,4-(CH$_3$)$_2$C$_6$H$_3$-

c, Ar=2,4-Br(CH$_3$)C$_6$H$_3$-; Ar'=2,4-(CH$_3$)$_2$C$_6$H$_3$-;

e, Ar=2,4-Br(CH$_3$)C$_6$H$_3$-; Ar'=3,4-(CH$_3$)$_2$C$_6$H$_3$-

a, Ar=Ar'=2,4-(CH$_3$)$_2$-C$_6$H$_3$-

b, Ar=2,4-Br(CH$_3$)C$_6$H$_3$-;
   Ar'=2,4-(CH$_3$)$_2$C$_6$H$_3$

c, Ar=2,4-Br(CH$_3$) C$_6$H$_3$-;
   Ar'=3,4-(CH$_3$)$_2$C$_6$H$_3$-

Ar = 2,4-(CH₃)₂C₆H₃-
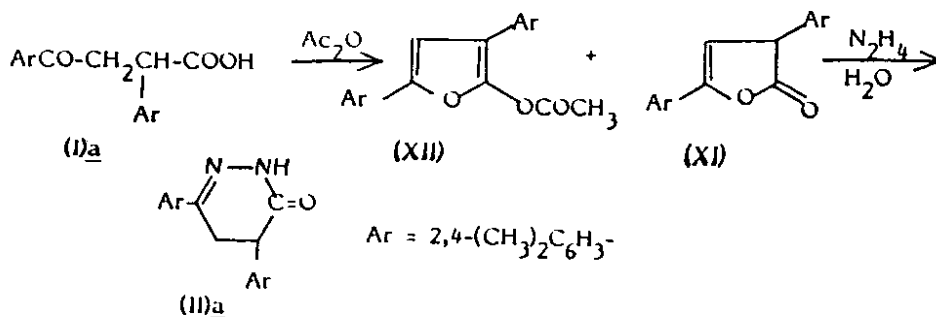
(XII) reacted with hydrazine hydrate affording a mixture of the pyridazinone (II)a and diacetylhydrazine, which were identified by m.p. and mixed m.p. determination. Similarly, (XII) reacted with phenyl-hydrazine producing 2-N-phenylpyridazin-3-one (III)a and acetyl phenyl-hydrazine.

Experimental

The infrared absorption spectra were determined with Pye Unicam 633791 and Perken Elmar 683 spectrophotometers using KBr Wafer technique. The NMR spectra were determined by a Varian (60 MHZ), using TMS as internal standard. Characterization data of all the compounds prepared are given in Table 1.

Formation of α-aryl-β-aroylpropionic acids (I)a-e

A solution of β-aroylacrylic acids (0.01 mole), hydrocarbon (0.01 mole) in acetylene tetrachloride (70 ml) was saturated with dry hydrogen chloride gas then AlCl₃ (0.04 mole) was added.

The reaction mixture was refluxed for 3 hrs. on a water bath with continuous stirring and then allowed to stand at room temperature overnight. The reaction mixture was then added to HCl-ice (20 ml conc. HCl/100 gm ice). Acetylene tetrachloride was removed by distillation. The residual materials were fractionally crystallized from the suitable solvent to give the corresponding α-aryl-β-aroyl pripionic acids

(I)a-e. The results are listed in table-1.

Formation of 4-aryl-6-(substituted)-aryl-2,3,4,5-tetrahydropyridazin-3-ones (II)a-e.

A solution of α-aryl-β-aroyl propionic acids (I)a-e (0.01 mole) in ethanol (50 ml) and hydrazine hydrate (0.01 mole) was refluxed for 6 hrs. The solids that separated after concentration and cooling were crystallized from the suitable solvent to give the pyridazinones (II)a-e.

Formation of 2N-(substituted)-4,6-diaryl-2,3,4,5-tetrahydropyridazin-3-ones (III)a-e.

A solution of propionic acids (II)a,c (0.01 mole) and N-substituted hydrazines namely, phenylhydrazine; 2,4-dinitrophenylhydrazine; semi-carbazide and/or salicyloylhydrazine (0.01 mole) in boiling ethanol (50 ml) gave a product which was filtered off and crystallized from the proper solvent to give the corresponding pyridazin-3-one derivatives (III)a,e.

Synthesis of 3-chloropyridazine derivative (IV)

A suspension of (II)a (1 g 0.026 mole) POCl₃ (3 ml) and PCl₅ (0.5 g) was heated on a steam bath for 2 hrs. The reaction mixture was poured gradually into crushed ice (ca, 150 g), the solid that separated was filte-

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Table-1: Characterization data of compounds prepared

Compd.	M.P.°C & Colour	Solvent & yield	Formula (M.W.)		Analysis % Calcd.	Found
(I)a	128	Pet.60-80°	$C_{20}H_{22}O_3$	C	77.41	77.50
	White	(90)	(310)	H	7.09	6.90
b	125	Pet.60-80°	$C_{22}H_{26}O_3$	C	78.10	78.31
	White	(88)	(338)	H	7.69	7.42
c	128	Pet.60-80°	$C_{19}H_{19}O_3Br$	C	60.80	60.62
	White	(85)	(375)	H	5.06	4.91
d	126	n-Hexane	$C_{19}H_{19}O_3Br$	C	60.80	60.53
	White	(90)	(375)	H	5.06	4.81
e	125	Pet.60-80°	$C_{19}H_{19}O_3Br$	C	60.80	61.02
	White	(85)	(375)	H	5.06	5.30
(II)a	139	Ethanol	$C_{20}H_{22}N_2O$	C	78.43	78.71
	White	(75)	(306)	H	7.18	6.93
				N	9.15	9.31
b	167	Ethanol	$C_{22}H_{26}N_2O$	C	79.04	78.80
	White	(80)	(334)	H	7.78	7.43
				N	8.38	8.63
c	108	Ethanol	$C_{19}H_{19}N_2OBr$	C	61.45	61.60
	White	(80)	(371)	H	5.12	5.00
				N	7.54	7.81
d	106	Ethanol	$C_{19}H_{19}N_2OBr$	C	61.45	61.65
	White	(80)	(371)	H	5.12	5.40
				N	7.54	7.31
e	120	Ethanol	$C_{19}H_{19}N_2OBr$	C	61.45	61.67
	White	(75)	(371)	H	5.12	5.50
				N	7.54	7.31
(III)a	125	Ethanol	$C_{26}H_{26}N_2O$	C	81.67	81.41
	White	(75)	(382)	H	6.80	6.81
				N	7.32	7.11
b	126	Ethanol	$C_{25}H_{23}N_2OBr$	C	67.11	67.21
	White	(70)	(447)	H	5.14	5.00
				N	6.26	6.42

Table-1 (Cont.)

Compd.	M.P.°C & Colour	Solvent & yield	Formula (M.W.)		Analysis % Calcd.	Found
c	131	Ethanol	$C_{26}H_{24}N_4O_5$	C	66.10	65.85
	White	(80)	(472)	H	5.08	4.95
				N	11.86	11.66
d	124	Ethanol	$C_{21}H_{23}N_3O_2$	C	72.20	72.41
	White	(80)	(349)	H	6.59	6.75
				N	12.03	11.93
e	136	Ethanol	$C_{27}H_{26}N_2O_3$	C	76.05	75.92
	White	(85)	(426)	H	6.10	5.95
				N	6.57	6.77
(IV)	206	Ethanol	$C_{20}H_{21}N_2Cl$	C	73.95	73.75
	colourless	(65)	(324.5)	H	6.47	6.60
				N	8.62	8.40
(V)	145	Ethanol	$C_{20}H_{21}N_5$	C	72.50	72.32
	White	(60)	(331)	H	6.34	6.61
				N	21.14	20.93
(VI)a	233	Butanol	$C_{27}H_{26}N_4$	C	79.80	79.60
	White	(80)	(406)	H	6.40	6.80
				N	13.79	13.65
b	150	Ethanol	$C_{27}H_{26}N_4O$	C	76.77	76.50
	White	(85)	(422)	H	6.16	5.94
				N	13.27	13.10
c	250	Ethanol	$C_{26}H_{25}N_4$	C	79.38	79.12
	White	(80)	(393)	H	6.36	6.61
				N	14.24	14.50
(VII)a	152	Ethanol	$C_{22}H_{24}N_2O_2$	C	75.86	75.92
	White	(75)	(348)	H	6.89	6.72
				N	8.04	8.22
b	155	Toluene	$C_{22}H_{23}N_2O_2Cl$	C	69.01	68.85
	White	(65)	(382.5)	H	6.01	6.23
				N	7.32	7.10
(VIII)	160	Ethanol	$C_{20}H_{20}N_2S$	C	75.00	75.20
	Yellow	(85)	(320)	H	6.25	6.10
				N	8.75	8.60

Table-1 (Cont.)

Compd.	M.P.°C & Colour	Solvent & yield	Formula (M.W.)		Analysis % Calcd.	Found
(IX)	198	Toluene	$C_{27}H_{27}N_3$	C	82.44	82.72
	White	(70)	(393)	H	6.87	6.65
				N	10.68	10.90
(X)a	214	Ethanol	$C_{20}H_{20}N_2O$	C	78.94	78.71
	White	(88)	(304)	H	6.57	6.50
				N	9.21	9.42
b	204	Ethanol	$C_{19}H_{17}N_2OBr$	C	61.78	61.50
	White	(80)	(369)	H	4.60	4.41
				N	7.58	7.42
c	207	Ethanol	$C_{19}H_{17}N_2OBr$	C	61.78	61.95
	White	(75)	(369)	H	4.60	4.83
				N	7.58	7.41
(XI)	205	Acetic acid	$C_{20}H_{20}O_2$	C	82.19	81.93
	White	(70)	(292)	H	6.84	6.68
(XII)	98	Pet.40-60°	$C_{22}H_{22}O_3$	C	79.04	79.20
	White	(85)	(334)	H	6.58	6.30

red off and crystallized from the proper solvent and gave the chloropyridazine derivative (IV).

Formation of tetrazolopyridazine (V)

A solution of (IV) (0.01 mole) in ethanol (50 ml) and sodium azide (1 g), was refluxed for 10 hrs. The solid that separated was crystallized from the suitable solvent and gave tetrazolopyridazine (V).

Formation of triazolopyridazine (VI)

A solution of (IV) (0.01 mole) in butanol (50 ml) and acylhydrazines namely, benzoylhydrazine, nicotinoylhydrazine and/or salicyloyl hydrazine (0.01 mole) was refluxed for 6 hrs. The solids that separated were crystalized from the suitable solvent and gave triazolopyridazine derivatives (VI).

*Formation of 3-acylpyridazines (VII)
a & b*

A mixture of solid (II)a (0.01 mole) and acyl chloride (10 ml) was treated with few drops of piperidine then refluxed on water bath for half hr., then cooled. The product was treated with crushed ice and the separated solid was crystallized from the suitable solvent and gave the corresponding 3-acylpyridazine (VII) a & b.

Formation of the pyridazin-3-thione (VIII)

A solution of (II)a (0.01 mole), phosphorus pentasulfide (0.02 mole), and dry xylene (50 ml) was refluxed for 30 min. The reaction mixture was filtered upon hot and the solid that separated upon concentration and cooling was crystallized from the proper solvent and gave the thione (VIII).

Formation of 3N-benzylpyridazine (IX)

A solid of (II)a (0.01 mole) and excess benzylamine was fused at m.p. of (II)a for 3 hrs. The product was crystallized from toluene to give 3N-benzylpyridazine (IX).

Formation of the dihydropyridazinone derivatives (X)a-c

A vigorously stirred (II)a,c & e) (0.01 mole) in glacial acetic acid (50 ml) was heated to 50–60°C and then treated portion-wise with bromine (0.01 mole) during a period for 3 hrs., and then poured on ice/water. The solid that separated was filtered off and crystallized from the suitable solvent to give (IX)a-c. The results recorded in Table 1.

Conversion of O-aryl-3-aroylpropionic acid (I)a to butenolide (XI) and the 2-acetoxy-3,5-diarylfuran (XII).

A solution of propionic acid derivative (I)a (0.01 mole) in acetic anhydride (30 ml) was warmed for 3 hrs. on water bath. The solid obtained after cooling and scratching was crystallized from the suitable solvent to give (XI) and XII).

Reaction of butenolide (XI) with hydrazine hydrate: Formation of pyridazine (II)a

A solution of butenolide (XI) (0.01 mole) in ethanol (50 ml) and hydrazine hydrate (0.01 mole) was refluxed for 3 hrs. The solid product obtained after cooling and crystallized from ethanol gave the pyridazine (II)a.

Formation of diacetylhydrazine with (II)a or 2N-phenyl pyridazine-3-ones with (III)a.

A solution of acetoxy furan (XII) (0.01 mole) in ethanol (50 ml) and hydrazine hydrate or phenylhydrazine (0.01 mole) was refluxed for 3 hrs. The solid product separated was filtered off and fractionally crystallized giving diacetylhydrazine or acetyl phenylhydrazine. The mother liquors were concentrated and cooled. The separated solids were filtered off and recrystallized from ethanol to give the pyridazinones (II)a or (III)a.

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