

## Alkylation of Indole with $\beta$ -Aroylacrylic Acids and some Studies on the Alkylated Products

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**Summary:**  $\beta$ -Aroyl- $\alpha$ -(indole-3-yl) propionic acids (II) were prepared by the reaction of  $\beta$ -aroyl-acrylic acids (I) with indole. Reaction of (II) with hydrazines afforded the pyridazinones (III) and (IV). Pyridazinone (III) reacted with  $\text{POCl}_3$ , ethylbromoacetate and  $\text{P}_2\text{S}_5$  to yield chloropyridazine (V), 3-O-carbethoxymethyl pyridazine (VIII) and the thione derivatives (XII) respectively. The behaviour of 3-chloropyridazine towards hydrazine hydrate and acyl hydrazines was investigated. Actions of hydrazine hydrate and benzylamine on the 3-O-carbethoxymethyl pyridazine and thione (VIII) and (XII) were also investigated. Dehydration of (II) yielded the butenolide (XV). The behaviour of the butenolide towards benzylamine, ammonium acetate and hydroxylamine hydrochloride was studied.

A large number of pyridazinones are reported to exhibit insecticidal [1,2] and bactericidal activities [3]. This prompted us to synthesise a new series of corresponding pyridazinones (see scheme 1-6).

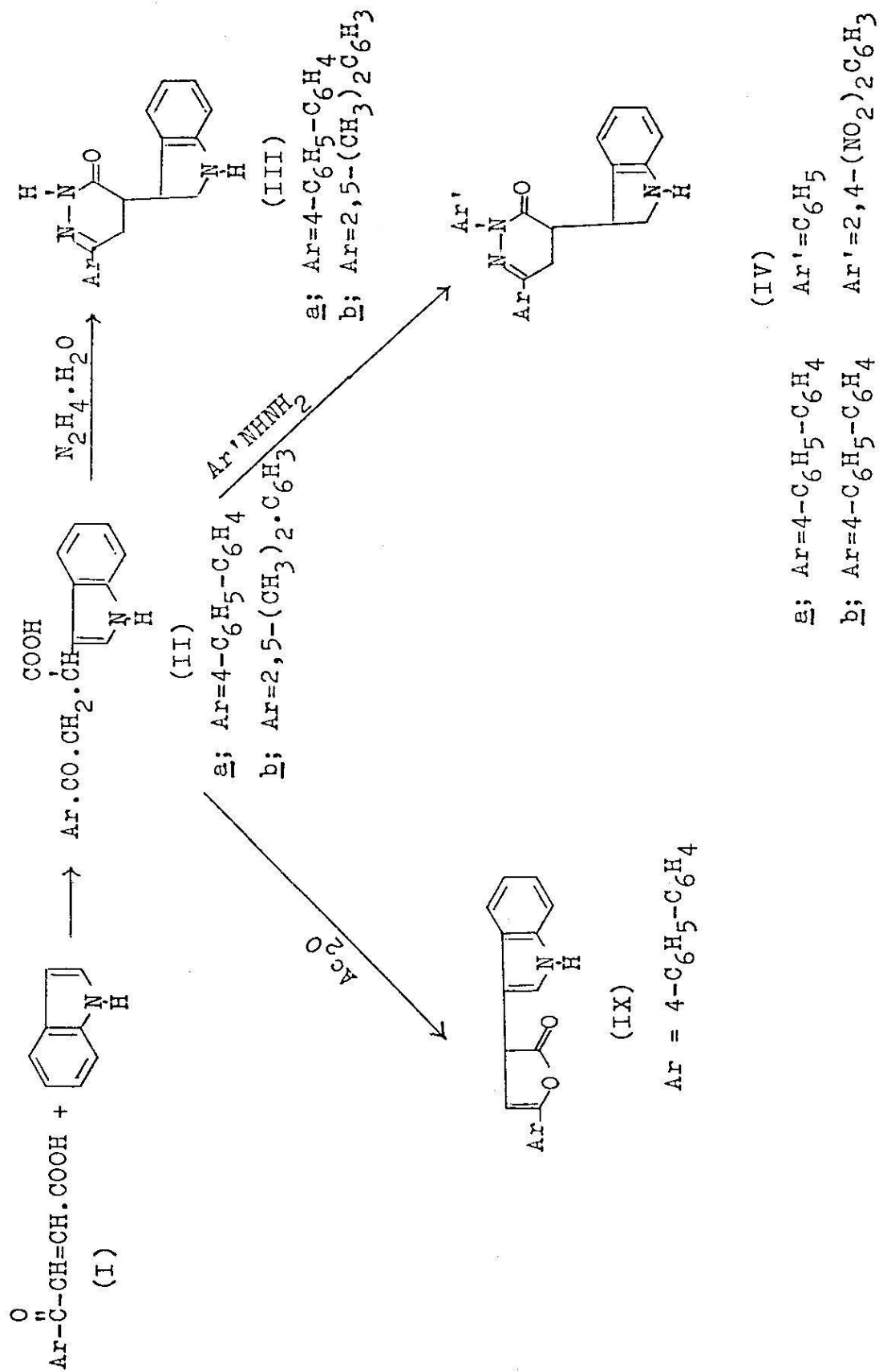
The reaction of 4-phenyl-(1a)-2,5-dimethyl-(1b)-3-benzoyl-acrylic acids with indole in dry benzene gave  $\beta$ -aroyl- $\alpha$ -(indole-3-yl)-propionic acids (IIa and b).

The condensation of the acids (IIa and b) with hydrazine hydrate, phenylhydrazine or 2,4-dinitrophenylhydrazine yielded the corresponding 4,6-disubstituted-2,3,4,5-tetrahydropyridazin-3-ones (IIIa) and (b) and 2,4,6-trisubstituted-2,3,4,5-tetrahydropyridazin-3-ones (IVa and b), respectively [4-7].

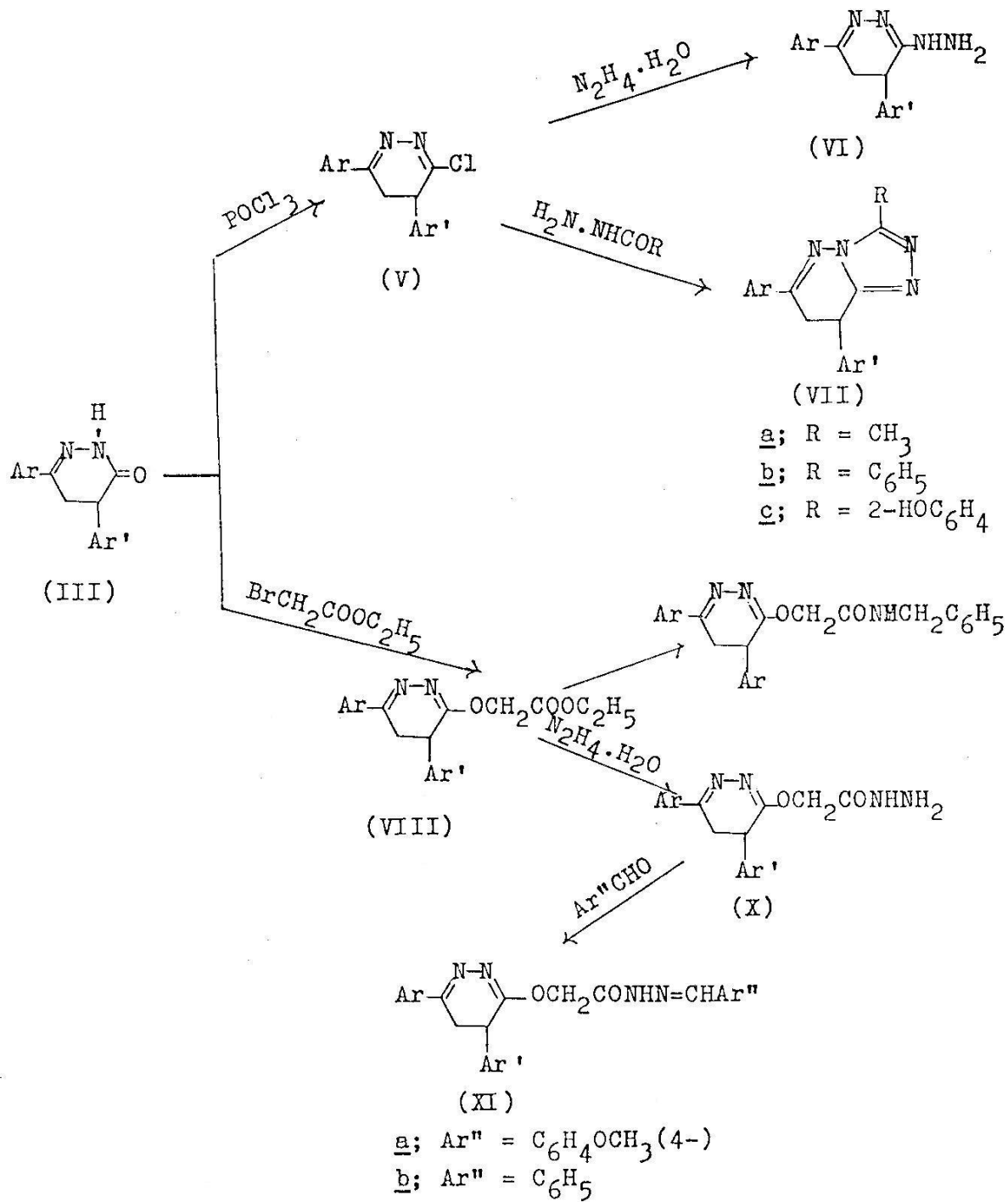
Recently [8], it was reported that pyridazinones actually exist as equilibrium and this has been confirmed

by studying the behaviour of pyridazinone derivative (IIIa) towards nucleophilic reagents like  $\text{POCl}_3$ . Thus treatment of (IIIa) with  $\text{POCl}_3$  gave the 3-chloropyridazine derivative (V). The IR spectrum of (V) was devoid of  $\nu \text{C=O}$ . In this investigation, the behaviour of the chloropyridazine (V) towards different reagents has been described.

Treatment of (V) with hydrazine hydrate in boiling  $\text{C}_2\text{H}_5\text{OH}$  gave 3-hydrazino-4-(3'-indolyl)-6-biphenyl-4,5-dihydropyridazine (VI). In this investigation the hitherto unknown reaction of chloropyridazine derivative (V) with acyl hydrazines in refluxing butanol was performed. Reaction of (V) with acetylhydrazine, benzoylhydrazine or salicyloylhydrazine in refluxing 1-butanol gave triazolopyridazines (VIIa-c). The first step is attack of the nitrogen nucleophile at the C-Cl position, then followed by double bond



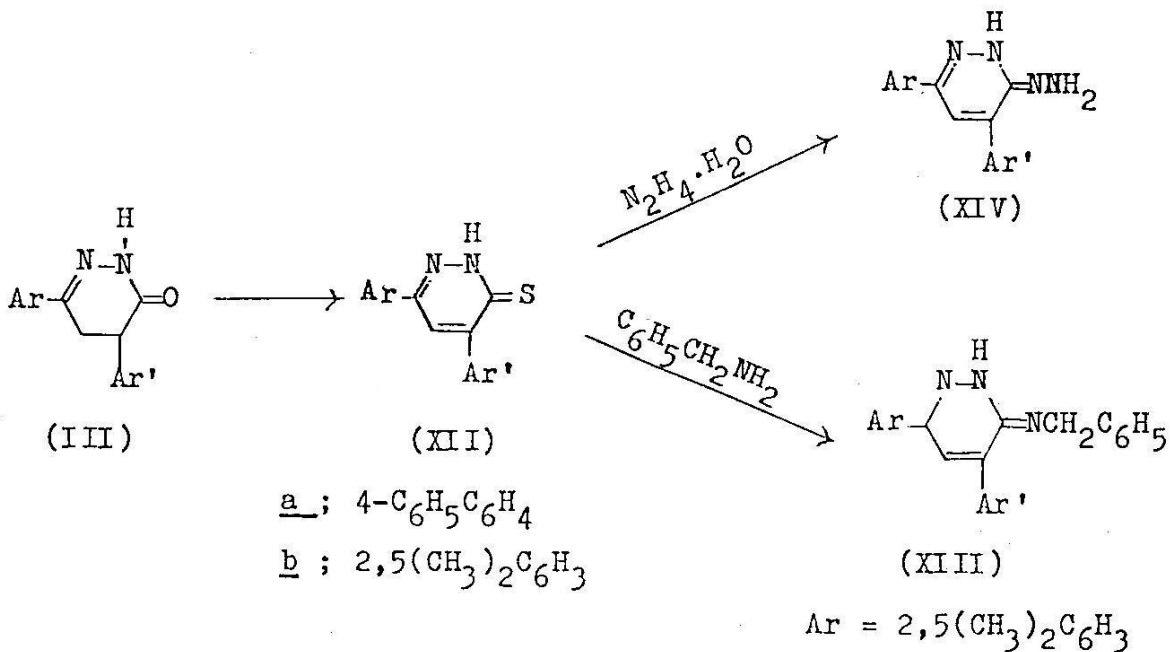
(Scheme 1)



Ar = 4-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>

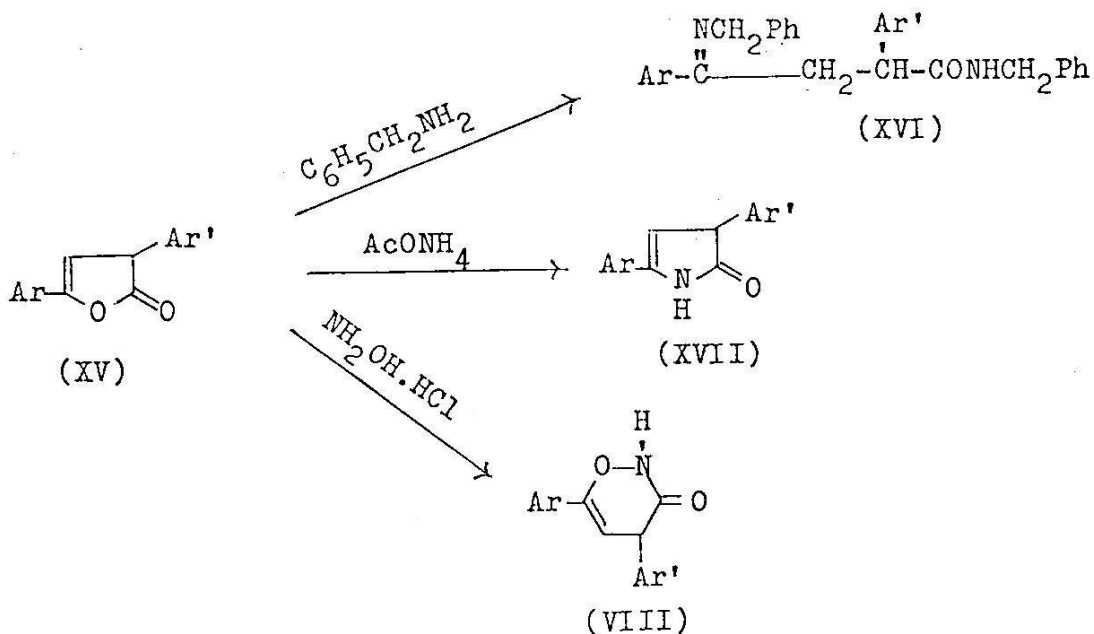
Ar' = 3-indolyl

(Scheme 2)



Ar' = 3-indolyl

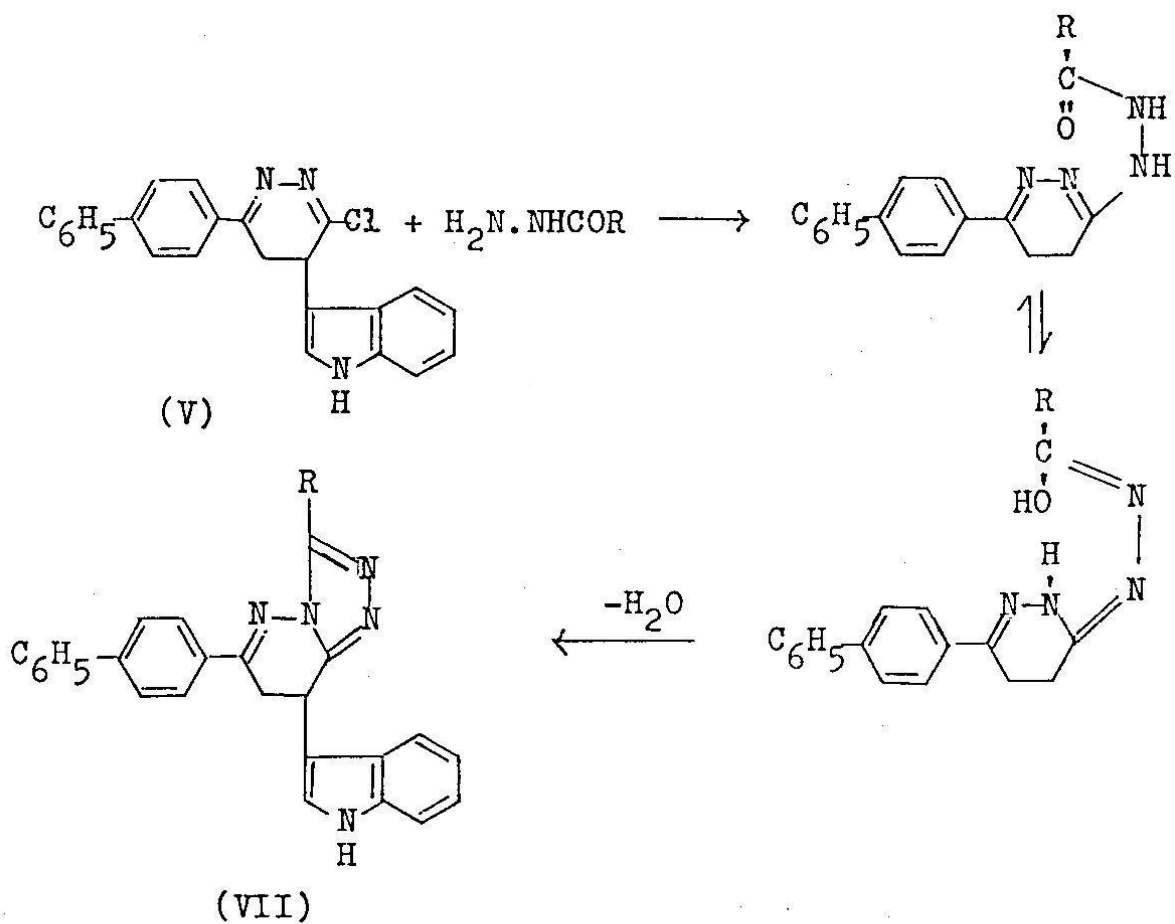
(Scheme 3)

Ar = 4-C<sub>6</sub>H<sub>5</sub>C<sub>6</sub>H<sub>4</sub>

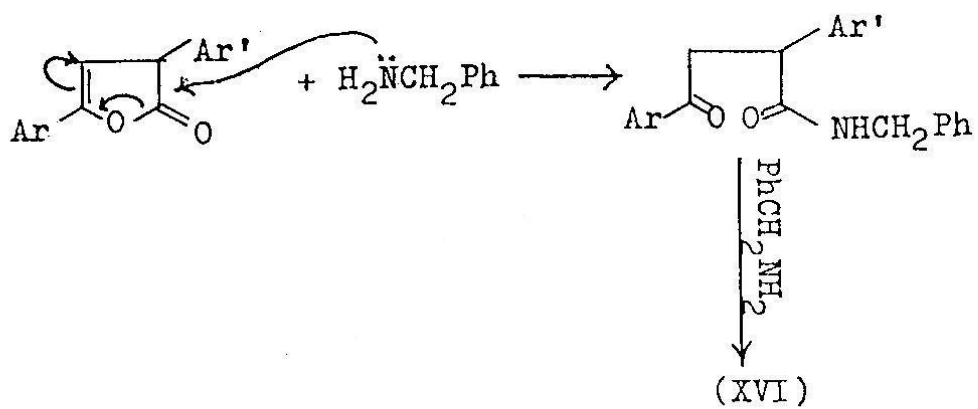
Ar' = 3-indolyl

(Scheme 4)

Alkylation of Indole



(Scheme 5)



(Scheme 6)

migration with proton transfer and loss of one molecule of water. In this case the fact, that, migration of  $\pi$ -bond leads directly to configuration easily cyclised and thermodynamically stable intermediate which contributes to driving force of the reaction (see scheme 5). The evidence for compound (VIIa) was obtained by independent synthesis via the reaction of (VI) with ethyl orthoacetate in boiling butanol.

The pyridazinones could be alkylated in good yield with a variety of electrophilic reagents. Thus, treatment of (IIIa) with ethylbromoacetate in refluxing acetone in presence of potassium carbonate gave 3-O-carbethoxymethyl pyridazine derivative (VIII). The evidence for the structure of (VIII) was obtained by its reaction with benzylamine and hydrazine hydrate to give the N-benzylcarboxamide (IX) and the acetic acid hydrazide (X) derivatives, respectively.

The aim of this work also is to synthesis of some imine derivatives containing pyridazine nucleus, in the hope of their biochemical effect. Thus condensation of (X) with anisaldehyde and benzaldehyde in boiling ethanol afforded the imine derivatives (XIa and b).

Reaction of the pyridazinone derivative (IIIa) and (b) with phosphorus pentasulfide in boiling xylene afforded 6-aryl-4(3-indolyl)-3-(2H)-pyridazine thiones (XIIIa) and (XIIIb), respectively via thionation-dehydrogenation reactions. The structure of (XII) was confirmed by its reaction with benzylamine and hydrazine hydrate in refluxing alcohol to give the Schiff base (XIII) and the hydrazine (XIV) derivatives, respectively.

The  $\alpha$ -(3-indolyl)-3-biphenyl propionic acid (IIa) was easily dehydrated by boiling with acetic

anhydride or heating at their melting point to yield  $\gamma$ -biphenyl- $\alpha$ -(3-indolyl)- $\Delta^{\beta,\alpha}$ butenoilide (XV). The structure of (XV) was established from the following findings:

a) It is readily hydrolysed by hot alkali giving the corresponding acid (IIa).

b) Compound (XV) reacts with benzylamine in refluxing butanol to give Schiff base (XVI). The first step involving ring fission of (XV) by nitrogen nucleophile leads to formation of the intermediate (XVII). The latter underwent condensation with another molecule of benzylamine, the initial N-substituted hemiaminal loses water to give the stable Schiff base (XVI), as shown in scheme 6.

c) Compound (XV) reacts with ammonium acetate in boiling xylene to give 4-(3-indolyl)-2-biphenyl-2-pyrroline-5-one (XVIII).

d) Reaction of (XV) with hydrazine hydrate in boiling ethanol gave 4-(3-indolyl)-6-biphenyl-2,3,4,5-tetrahydropyridazin-3-one (IIIa) which was identified by m.p. and mixed m.p. determination.

e) Reaction of (XV) with hydroxylamine hydrochloride in boiling pyridine yielded 5-(3-indolyl)-3-biphenyl-1,2-dihydro-2,1-oxazin-6-one (XIX).

## Experimental

The infrared absorption spectra were determined with Pye Unicam 633791 spectrophotometer using KBr wafer technique. The PMR spectra were recorded with a varian (60 MHz), Jeol JNMFX 200 instrument, the position of peaks is expressed in ppm ( $\delta$ -values), TMS as internal standard. All melting points are uncorrected.

Table-1: Physical data of various compounds prepared

| Compd   | M.P.<br>°C | Yield<br>% | Mol.<br>Formula   | Found % |      |       | Required % |      |       |
|---------|------------|------------|---|---------|------|-------|------------|------|-------|
|         |            |            |   | C       | H    | N     | C          | H    | N     |
| (IIa)   | 194        | 80         | C <sub>24</sub> H <sub>19</sub> NO <sub>3</sub>               | 78.2    | 4.9  | 3.8   | 78.04      | 5.14 | 3.79  |
| (IIb)   | 112        | 70         | C <sub>20</sub> H <sub>19</sub> NO <sub>3</sub>               | 74.4    | 6.0  | 4.62  | 74.76      | 5.91 | 4.36  |
| (IIIa)  | 249        | 80         | C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O              | 79.0    | 5.4  | 11.7  | 78.96      | 5.20 | 11.5  |
| (IIIb)  | 173        | 70         | C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O              | 76.1    | 6.3  | 13.52 | 75.7       | 5.99 | 13.24 |
| (IVa)   | 228        | 60         | C <sub>30</sub> H <sub>23</sub> N <sub>3</sub> O              | 81.7    | 5.3  | 9.32  | 81.6       | 5.2  | 9.52  |
| (IVb)   | 204        | 60         | C <sub>30</sub> H <sub>23</sub> N <sub>3</sub> O              | 81.7    | 5.3  | 13.6  | 67.79      | 3.95 | 13.18 |
| (V)     | 260        | 40         | C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub>              | 75.1    | 4.8  | 11.0  | 75.09      | 4.69 | 10.95 |
| (VI)    | 223        | 80         | C <sub>24</sub> H <sub>21</sub> N <sub>5</sub>                | 75.58   | 5.2  | 18.26 | 75.98      | 5.54 | 18.46 |
| (VIIa)  | 271        | 70         | C <sub>26</sub> H <sub>21</sub> N <sub>5</sub>                | 77.41   | 4.85 | 17.50 | 77.41      | 5.21 | 17.36 |
| (VIIb)  | <300       | 60         | C <sub>31</sub> H <sub>23</sub> N <sub>5</sub> O              | 80.4    | 5.1  | 14.9  | 80.0       | 4.94 | 15.02 |
| (VIIc)  | 289        | 50         | C <sub>31</sub> H <sub>23</sub> N <sub>5</sub> O              | 76.9    | 4.4  | 14.7  | 77.33      | 4.78 | 14.55 |
| (VIII)  | 115        | 40         | C <sub>25</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> | 72.3    | 6.3  | 9.8   | 72.28      | 6.02 | 10.10 |
| (IX)    | 235        | 80         | C <sub>33</sub> H <sub>27</sub> N <sub>4</sub> O <sub>2</sub> | 77.2    | 5.3  | 10.6  | 77.49      | 5.28 | 10.95 |
| (X)     | <300       | 80         | C <sub>26</sub> H <sub>23</sub> N <sub>5</sub> O <sub>2</sub> | 71.6    | 5.4  | 16.1  | 71.39      | 5.26 | 16.01 |
| (XIa)   | 160        | 70         | C <sub>34</sub> H <sub>29</sub> N <sub>5</sub> O <sub>3</sub> | 73.2    | 5.4  | 12.3  | 73.51      | 5.22 | 12.61 |
| (XIb)   | 95         | 75         | C <sub>33</sub> H <sub>27</sub> N <sub>5</sub> O <sub>2</sub> | 75.14   | 5.3  | 13.2  | 75.42      | 5.14 | 13.33 |
| (XIIa)  | 189        | 50         | C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> S              | 75.3    | 5.1  | 10.8  | 75.59      | 4.98 | 11.02 |
| (XIIb)  | 169        | 53         | C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> S              | 71.9    | 5.4  | 12.4  | 72.07      | 5.70 | 12.61 |
| (XIII)  | 223        | 60         | C <sub>27</sub> H <sub>26</sub> N <sub>4</sub>                | 79.65   | 6.2  | 13.5  | 79.8       | 6.4  | 13.79 |
| (XIV)   | 203        | 65         | C <sub>20</sub> H <sub>21</sub> N <sub>5</sub>                | 72.3    | 6.1  | 21.3  | 72.5       | 6.34 | 21.14 |
| (XV)    | 254        | 70         | C <sub>24</sub> H <sub>17</sub> NO <sub>2</sub>               | 81.9    | 4.4  | 4.2   | 82.05      | 4.84 | 3.98  |
| (XVI)   | 190        | 70         | C <sub>37</sub> H <sub>33</sub> N <sub>3</sub> O              | 81.6    | 5.9  | 7.63  | 82.99      | 6.16 | 7.85  |
| (XVII)  | 147        | 80         | C <sub>24</sub> H <sub>18</sub> N <sub>2</sub> O              | 82.5    | 5.0  | 7.8   | 82.88      | 5.14 | 8.0   |
| (XVIII) | 194        | 60         | C <sub>24</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> | 78.5    | 4.7  | 7.5   | 78.68      | 4.91 | 7.65  |

*Synthesis of (Ia) and (Ib)*

$\beta$ -4-phenylbenzoylacrylic acid (Ia) and  $\beta$ -2,5-dimethylbenzoyl-acrylic acid (Ib) were prepared as shown in the literature [9].

*Alkylation of indole with  $\beta$ -aroylacrylic acid: Formation of (IIa) and (b)*

To a solution of (Ia) and (b) (0.01 mol) in dry benzene (20 ml), was added indole (0.01 mol) and the reaction mixture refluxed for 10 hrs. The solid that separated on cooling was crystallized from methanol to give (IIa) and from light pet. (60-80) respectively.

*PMR (CDCl<sub>3</sub>) of (IIb)*

$\delta$  7.5-7.1 (7H, m, Ar-H),  $\delta$  4.8-4.5 (1H, m, CH of indole),  $\delta$  4.1-3.7 (1H, q, -CH<sub>2</sub>-CH<, J = 5 Hz),  $\delta$  3.3-2.99 (2H, m, none-equivalent -CH<sub>2</sub><) and at 2.4-2.3 (6H, s, two -CH<sub>3</sub>).

*Reaction of (IIa), (b), (V), (VIII), (XII) and (XV) with hydrazines and amines: Formation of (IIIa) and (b), (IVa) and (b), (VI), (IX), (X), (XIII), (XIV) and (XVI)*

A mixture of (IIa), (b), (V), (VIII), (XII) or (XV) (0.01 mol) and hydrazine hydrate, phenylhydrazine, 2,4-dinitrophenylhydrazine or benzylamine (0.015 mole) in ethanol or butanol (20 ml) was refluxed for 3 hours.

The solid that separated after concentration and cooling was crystallized from ethanol to give (IIIa), (IIIb), (IVa), (X), (XIII), (XIV), from acetic acid to give (IVb), from methanol to give (VI) and from benzene/light pet. (60-80) to give (XVI).

*PMR (CDCl<sub>3</sub>) of (IIIb)*

$\delta$  7.3-7.0 (7H, m, Ar-H),  $\delta$  4.8-4.5 (1H, m, CH of indole),  $\delta$  4.2-3.6 (1H, q, -CH<sub>2</sub>-CH, J = 6.4 Hz),  $\delta$  3.3-3.0 (2H, t, non-equivalent CH<sub>2</sub>-CH, J = 4.8 Hz) and at  $\delta$  2.3-2.1 (6H, s, 2CH<sub>3</sub> groups).

*Reactions of (IIIa) with POCl<sub>3</sub>: Formation (V)*

A mixture of (IIIa) (0.01 mol) and POCl<sub>3</sub> (10 ml) was gently refluxed for 30 min cooled, treated with crushed ice and the precipitated solid filtered and crystallized from ethanol to give (V).

*Reaction of (V) with acylhydrazines: Formation of triazolopyridazines (VIIa-c)*

A solution of (V) (0.01 mol) in butanol (50 ml) was treated with acylhydrazine, namely acetylhydrazine, benzoylhydrazine and salicyloylhydrazine (0.01 mol) was refluxed for 60 hrs. The solid that separated on cooling was crystallized from acetic acid to give (VIIa-c) respectively.

*PMR (DMSO) of (VII)*

$\delta$  7.8-7.1 (14H, m, Ar-H),  $\delta$  4.4-4.6 (2H, d, 2H at C<sub>5</sub>, J = 5 Hz),  $\delta$  4.3-4.05 (5H, m, -C-CH-CH<sub>3</sub> and -O-CH<sub>2</sub>-C<sup>O</sup>,  $\delta$  3.4-3.2 (1H, d, 1H at C<sub>4</sub>, J = 6.6 Hz) and at  $\delta$  1.3-1.1 (3H, s, -CH<sub>3</sub>).

*Independent synthesis of (VIIa)*

A mixture of 3-hydrazino-pyridazine (VI) (0.01 mol) and ethyl orthoacetate (0.02 mol) in butanol (50 ml) was heated under reflux for 5 hrs. The solid that separated after concentration



Table-2: The infrared of some new compounds

| Compound | Group frequencies (KBr; $\text{cm}^{-1}$ )   |
|----------|--|
| (IIa,b)  | $\nu\text{C}=\text{O}$ (carboxyl) at 1720-1710, $\nu\text{C}=\text{O}$ (ketone) at 1690-1670                                     |
| (IIIa,b) | $\nu\text{C}=\text{O}$ (cyclic amide) at 1720-1670, $\nu\text{NH}$ (3420-3240)   |
| (VI)     | $\nu\text{C}=\text{O}$ (1740), $\nu\text{C}=\text{N}$ (1660), $\nu\text{NH}$ (3300)  |
| (VII)    | $\nu\text{C}=\text{O}$ (1740), $\nu\text{C}=\text{N}$ (1660), $\nu\text{NH}$ (3300)  |
| (IX)     | $\nu\text{C}=\text{O}$ (amide) at 1660, $\nu\text{C}=\text{N}$ (1610), $\nu\text{NH}$ (3300)                                     |
| (X)      | $\nu\text{C}=\text{O}$ (1670), $\nu\text{C}=\text{N}$ (1600), $\nu\text{NH}$ (3000)  |
| (XI)     | $\nu\text{C}=\text{O}$ (1660), $\nu\text{C}=\text{N}$ (imine) at 1650, $\nu\text{C}=\text{N}$ (1610), $\nu\text{NH}$ (3300-3240) |
| (XIII)   | $\nu\text{C}=\text{N}$ (1620), $\nu\text{NH}$ (3440)   |
| (XV)     | $\nu\text{C}=\text{O}$ (lactone) at 1760   |
| (XVI)    | $\nu\text{C}=\text{O}$ (1670), $\nu\text{C}=\text{N}$ (1640), $\nu\text{NH}$ (3400)  |
| (XVIII)  | $\nu\text{NH}$ (3410-3205), $\nu\text{C}=\text{O}$ (1675), $\nu\text{C}=\text{N}$ (1620)   |

and cooling was identified as (VIIa) by m.p and mixed m.p. determinations.

*Reaction of (IIIa) with ethylbromoacetate. Formation of (VIII)*

A mixture of (IIIa) (0.01 mol) anhydrous potassium carbonate (0.03 mol), ethylbromoacetate (0.03 mol) and dry acetone (50 ml) was refluxed for 20 hours. After removing the excess solvent the product was crystallized from light petroleum to give (VIII).

*Condensation of (X) with aromatic aldehydes: Formation of imines (IXa) and (b)*

A solution of (X) (0.01 mol), anisaldehyde or benzaldehyde (0.01 mol) in ethanol (50 ml) was heated under reflux for 6 hours. The products that separated on cooling were crystallized from benzene to give (IXa) and from light pet. (60-80) to give (XIb).

*Action of  $\text{P}_2\text{S}_5$  on the pyridazinones (IIIa) and b: Formation of (XIIa) and b*

A solution of (IIIa) or (b) (0.01 mol),  $\text{P}_2\text{S}_5$  (0.02 mol), and dry xylene

(50 ml) was boiled under reflux for 30 min. The reaction mixture was filtered while hot and the solid that separated upon concentration and cooling was crystallized from ethanol to give (XIIa) and (XIIb) respectively.

*Conversion of acid (IIa) to butanolide (XV)*

*Method A*

A solution of acid (IIa) (0.01 mol) in acetic anhydride (20 ml) was refluxed for 4 hours. The solid obtained after concentration and cooling was crystallized from acetic acid to give the butanolide (XV).

*Method B*

The acid (IIa) (0.01 mol) was heated at its melting point for 30 min. and the resulting solid crystallized from acetic acid to give the butanolide (XV).

*Hydrolysis of the butanolide (XV): Formation of acid (IIa)*

A solution of (XV) (1 g) in ethanol (10 ml) was treated with sodium hydroxide (1 g in 5 ml water), then heated

under reflux for 2 hours. The cooled solution was acidified with dilute HCl and the precipitate was crystallized from methyl alcohol and identified as (IIa) by m.p. and mixed m.p. determination.

*Reaction of butenolide (XV) with ammonium acetate: Formation of (XVII)*

A mixture of butenolide (XV) (0.01 mol), ammonium acetate (0.04 mol) was refluxed in xylene (50 ml) for 15 hours. The reaction mixture was poured into ice, and excess solvent was removed by steam distillation. The solid that separated was crystallized from benzene to give (XVII).

*Reaction of butenolide (XV) with hydroxylamine hydrochloride: Formation of (XVIII)*

A mixture of (XV) (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in pyridine (50 ml) was heated under reflux for 10 hours. The product separated after pouring the reaction mixture into ice-cold HCl was

crystallized from ethanol to give (XVIII).

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