Some Reactions with β-(3,4-dimethylbenzoyl)- α-(indol-3-yl)propionic acid and Screening of their Antibacterial Activities

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Summary: β-(3,4-dimethylbenzoyl)acrylic acid (I) reacts with indole to give β-(3,4-dimethylbenzoyl)-α-(indol-3-yl)propionic acid (2). The condensation of 2 with hydrazines affords the corresponding pyridazinones. Reactions of pyridazinones with N,N-*p*-(dimethylamino)benzaldehyde, acetyl chloride, benzenesulfonyl chloride, monochloroacetic acid, ethyl chloroformate gave the 4,5,6-trisubstituted pyridazinones and the N-substituted pyridazinone derivatives.

Reactions of pyridazinones with $POCl_3$ and P_2S_5 gave the chloro- and the thiopyridazine derivatives, which are subjected to further studies with anthranilic acid, *p*-anisidine, sodium azide, hydrazine hydrate and benzylamine.

The in-vitro antibacterial screening revealed that some of the new compounds possess activity against Gram-positive, Gram-negative bacteria and fungi.

Introduction

A large number of pyridazinones are reported to exhibit insecticidal [1], herbicidal [2], allergenic [3], antihypertensive [4] and bactericidal activities [5]. This prompted us to synthesize a new series of pyridazinones through the nucleophilic addition of indole to β-(3,4-dimethylbenzoyl)acrylic acid 1 followed by cyclisation of the adduct to pyridazinones and to screen the antibacterial activities of some of these new compounds.

The synthesis of various compounds is outlined in Scheme 1.

Thus, the reaction of β-(3,4-dimethylbenzoyl) acrylic acid (1) with indole gave β-(3,4-dimethylbenzoyl)-α-(indol-3-yl)propionic acid (2). The structure of (2) was derived from its IR* spectrum showing νC=O (acid) at 1705, νC=O at 1665, νC=N at 1600 and νNH 3420. The PMR (DMSO-d_6) spectrum of

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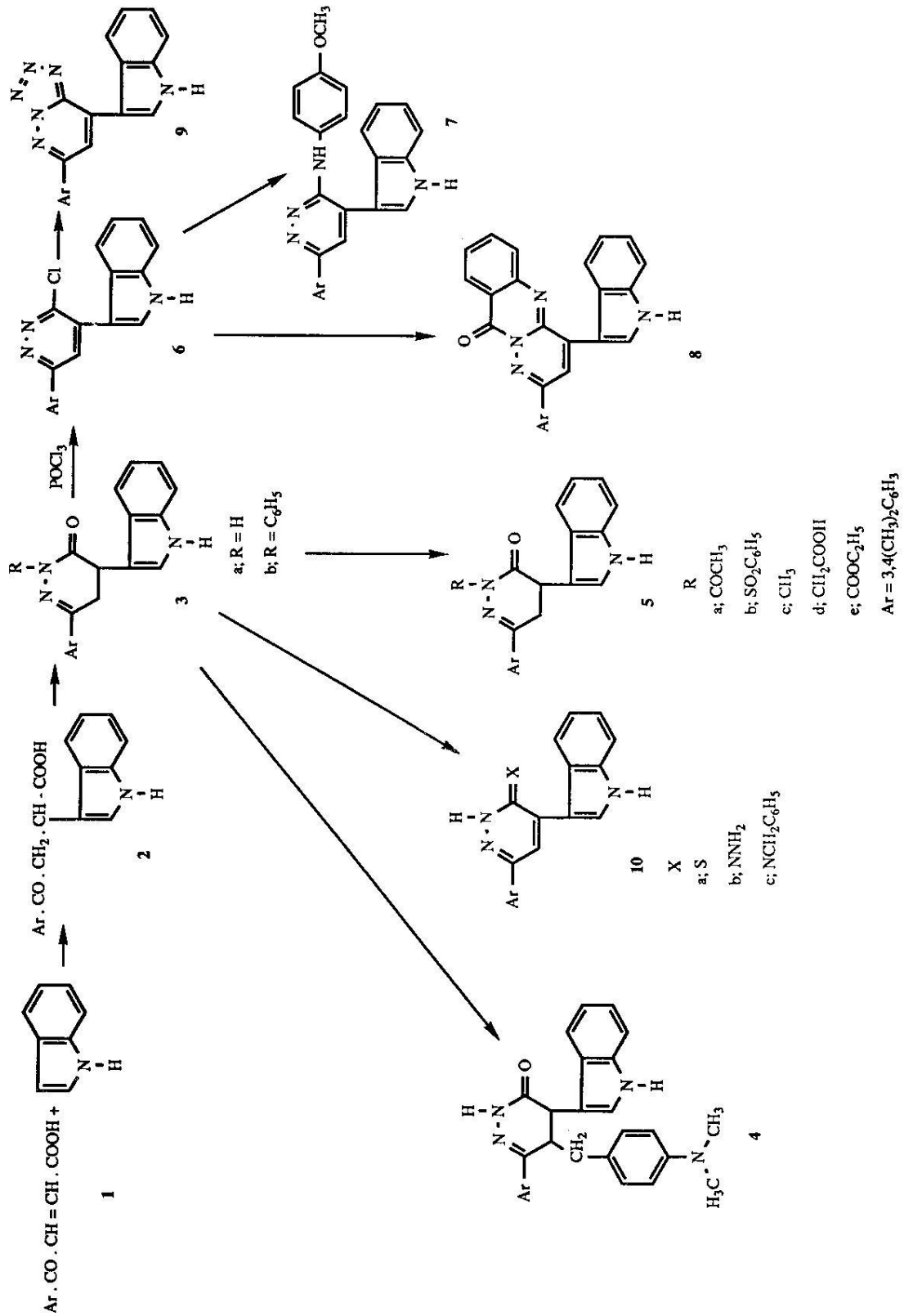
Ar . CO . CH = CH . COOH +
1
Ar . CO . CH2 . CH - COOH
2
3
a; R = H
b; R = C6H5
POCl3
6
7
8
9
5
R
a; COCH3
b; SO2C6H5
c; CH3
d; CH2COOH
e; COOC2H5
Ar = 3,4(CH3)2C6H3
10
X
a; S
b; NNH2
c; NCH2C6H5
4
H3C
CH3
Scheme -1

(2) showed signals at 8.00-7.60 (8H, m, Ar-H + NHCH), 4.20-3.40 (3H, m, CH_2- CH) and 2.4 (6H, s, $2CH_3$). The mass spectrum of (2) exhibited peaks at 321 (9.0%), 277 (16.8%), 174 (8.1%), 144 (33.2%), 133 (100%), 130 (2.9%), 117 (17.9%) and 105 (28.4).

The reaction of (2) with hydrazine hydrate, phenylhydrazine gave the pyridazinone derivatives (3a) and (3b), respectively. The structure of (3a) and (3b) was established on the basis of their elemental analyses and spectral data. Their IR spectra showed νC=O at 1655, νC=N at 1595 and νNH at 3350-3340. The PMR (DMSO-d_6) of (3a) exhibited signals at 7.80-7.00 (8H, m, Ar-H + NHCH), 4.10-3.25 (3H, m, CH_2- CH) and 2.2 (6H, s, $2CH_3$). The PMR (DMSO-d_6) of (3b) showed signals at 7.80-7.10 (13H, m, Ar-H + CH-NH), 4.30-3.35 (3H, m, CH_2-CH) and 2.3 (6H, s, $2CH_3$). The mass spectrum of 3a exhibited peaks at m/z 317 (50%), 289 (11.8%), 157 (100%), 143 (20.3%), 129 (30.5%), 117 (7.3%).

Condensation of (3a) with *p*-(N,N-dimethylamino) benzaldehyde took place at the 5-position to give the 4,5,6-trisubstituted pyridazinone derivative (4). Its IR spectrum showed νC=O at 1630, νC=N at 1585 and νNH at 3370.

The N-substituted derivatives (5a) and (5b) are obtained by the reaction of (3a) with acetyl chloride and benzensulphonyl chloride. Their IR spectra showed νC=O at 1685-1665, νC=N at 1605-1595 and νNH at 3430- 3270. Suprisingly, the reaction of chloroacetic acid with (3a) in ethanol in the presence of 20% aqueous NaOH gave the N-methylpyridazinone (5c) derivative and not the corresponding acid derivative (5d), presumably through the normal reaction followed by decarboxylation. Alternatively, compound (5c) can be obtained by methylation of pyridazinone (3a) with dimethylsulphate. The IR spectrum of (5c) showed νC=O at 1635, νC=N at 1595 and νNH at 3250. On the other hand, reaction of (3a) with ethylchloroformate in acetone in presence of potassium carbonate gave the ester derivative (5e). Its IR spectrum showed νC=O (ester) at 1730, νC=O at 1640, νC=N at 1595 and νNH at 3460.

Pyridazinone (3a) reacts with electrophilic reagents like $POCl_3$ to give the 3-chloropyridazine derivative (6), by substitution of the enolic hydroxyl group with chlorine together with dehydrogenation. The phenomenon of dehydrogenation is not strange since it is observed in the reaction of pyridazinones with P_2S_5 [6] and Grignard reagents. The IR spectrum of (6) showed νC=N at 1610 and νNH at 3080 and was devoid of νC=O. The PMR (DMSO-d_6) showed signals at 8.28-7.28 (9H, m, Ar-H + CH.NH + pyridazine proton) and 2.3 (6H, s, $2CH_3$). Compound (6) reacted with *p*-anisidine to give compound (7). Its infrared spectrum showed νC=N at 1605 and νNH at 3400.

Anthranilic acid reacted with (6) to give the quinazolinone derivative (8), its IR spectrum showed νC=O at 1745, νC=N at 1615 and νNH at 3400. Reaction of (6) with sodium azide in dimethylformamide gave the tetrazolopyridazine derivative (9). Its IR spectrum showed νC=N at 1600 and νNH at 3440.

Compound (3a) with P_2S_5 in dry xylene gave the corresponding thione (10a), a reaction in which thionation together with dehydrogenation take place. The IR spectrum showed νN-C=S at 1450, νC=S at 1385, νC=N at 1590 and νNH at 3400. The PMR (DMSO-d_6) of (10a) showed signals at 8.0-7.39 (9H, m, Ar-H + CHNH + pyridazine proton) and 2.4 (6H, s, $2CH_3$). Treatment of 10a with hydrazine hydrate yielded the corresponding hydrazone (10b). Its IR spectrum showed νC=N at 1585 and νNH at 3200. On the other hand, reaction of (10a) with benzylamine gave the Schiff base (10c). Its IR spectrum showed νC=N at 1585 and νNH at 3340.

Screening for antibacterial activity

In this study, the activity of the prepared compounds (2), (3a), (3b), (5c), (6) and (10a) was tested by the disk diffusion method [8]. Watmann No.1 filter paper disks were sterilized by autoclaving for one hour at 140°C. The sterile disks were impregnated with different compounds (200 mg/disk) Agar plates were surface inoculated uniformaly from fresh broth culture of *Staphylococcus aureus* (as strains Gram positive). *Escherichia coli* (as strains Gram negative) and *Aspergillus fumgytus* (as fungi). The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1 hour to permit good diffusion and then transferred to an incubator at 28°C for 24 hours. The zones of inhibition were then measured. The results are listed in Table 1.

Table 1: The antimicrobial activity of the synthesized compounds

Compound No.	*Staphylococcus aureus*	*Escherichia coli*	*Aspergillus fumgytus*
(2)	++	++	++
(3a)	++	++	+
(3b)	++	+	-
(5c)	++	++	+
(6)	+++	++	++
(10a)	++	++	+

+++ Highly sensitive (inhibition zone 12-15 mm)
++ Fairly sensitive (inhibition zone 9-12 mm)
+ Slightly sensitive (inhibition zone 6-9 mm)
- Not sensitive

From Table 1, it is clear that all compounds possess moderate activity against Gram positive except (6) which possesses high activity.

All compounds possess moderate activity against Gram negative except (3b) which possesses slight activity.

On the other hand, compounds (2) and (6) possess moderate activity against fungi, compounds (3a) and (10a) possess slightly activity while compound (3b) is not sensitive.

Experimental

Melting points are uncorrected. IR spectra (KBr) were recorded with a Unicam SP 1200 spectrophotometer. ^{1}H-NMR were measured with a Varian VN 1009 (S-60T) instrument using TMS as internal standard and mass spectra were measured with an AET-MS 902 mass spectrometer at 70eV, 6KV accelerating voltage at 130°C ion source temperature using a direct insertion probe.

Reaction of **(1)** *with indole. Formation of* **(2).**

To a solution of (1) (0.01 mole) in dry benzene (20 ml), indole (0.01 mole) was added and the reaction mixture refluxed for 10 hr. The solid that separated on cooling was crystallized from ethanol to give (2), m.p. 190°, yield 89% (Found: C, 74.93; H, 6.21; N, 4.19; $C_{20}H_{19}O_3$ requires: C, 74.74; H, 5.95; N, 4.35%).

Reaction of **(2), (6)** *and 10a with hydrazines, p-anisidine and benzylamine. Formation of* **(3a), (3b), (7), (10b)** *and* **(10c).**

To a solution of (2), (6) or (10a) (0.01 mole) in ethanol (20 ml), hydrazine hydrate, phenylhydrazine, *p*-anisidine or benzylamine (0.01 mole) was added and the reaction mixture refluxed for 5 h. The solid that separated on cooling was crystallized from ethanol **(3a, 7, 10b, 10c)** or benzene **(3b)**.

(3a): m.p. 215°C, yield 81% (Found: C, 75.43; H, 6.08; N, 13.52 $C_{20}H_{19}N_3O$ requires C, 75.68; H, 6.03; N, 13.24%).

(3b): m.p. 235°C, yield 75% (Found: C, 79.32; H, 5.97; N, 10.91 $C_{26}H_{23}N_3O$ requires C, 79.36; H, 5.89; N. 10.67%).

(7): m.p. 200°C yield 48% (Found: C, 77.35; H, 5.72; N, 13.50 $C_{27}H_{24}N_4O$ requires C, 77.11; H, 5.75; N, 13.32%).

(10b): m.p. 145°C, yield 45% (Found: C, 72.85; H, 6.10; N, 21.28; $C_{20}H_{19}N_5$ requires C, 72.92; H, 5.81; N, 21.26%).

(10c): m.p. 220°C, yield 47% (Found: C, 80.35; H, 6.20; N, 13.80$C_{27}H_{24}N_4$ requires C, 80.16; H, 5.98; N, 13.85%).

Reaction of **(3a)** *with p-(N-N-dimethylamino)benzaldehyde. Formation of* **(4).**

A warm solution of **(3a)** (0.01 mol) in ethanol (20 ml) was treated with ethanolic KOH solution (25 ml, 4%) and then *p*-(N,N-dimethylamino)benzaldehyde (0.01 mol) was added droopwise with continuous shaking. The reaction mixture was refluxed for 2 h, cooled, poured into cold water and the solid obtained was crystallized from ethanol to give **(4)**, m.p. 110°C yield 55% (Found: C, 77.48; H, 6.51; N, 12.37 $C_{29}H_{28}N_4O$ requires: C, 77.64; H, 6.29; N, 12.49%).

Reaction of **(3a)** *with acetyl chloride, benzenesulphonyl chloride dimethylsulphate and ethyl chloroformate. Formation of* **(5a-c)** *and* **(5e).**

A mixture **(3a)** (0.01 mole), anhydrous potassium carbonate (0.03 mol), acetyl chloride, benzenesulphonyl chloride dimethylsulphate or ethyl

chloroformate (0.03 mol) and dry acetone (50 ml) was refluxed for 24 h and excess solvent removed. The product was crystallized from ethanol (**5a,5e**) or benzene (**5b,5c**).

(**5a**): m.p. 110°C, yield 60% (Found: C, 73.73; H, 6.10; N, 11.72 $C_{22}H_{21}N_3O_2$ requires C, 73.51; H, 5.89; N, 11.69%).

(**5b**): m.p. 85°C, yield 55% (Found: C, 65.50; H, 4.92; N, 9.32; $C_{26}H_{23}N_3O_3S$ requires C, 68.24; H, 5.06; N, 9.18%).

(**5c**): m.p. 24°C, yield 45% (Found: C, 76.35; H, 6.52; N, 12.40 $C_{21}H_{21}N_3O$ requires C, 76.10; H, 6.38; N, 12.67%).

(**5e**): m.p. 235°C, yield 52% (Found: C, 71.20; H, 5.83; N, 10.82 $C_{23}H_{23}N_3O_3$ requires C, 70.93; H, 5.95; N, 10.79 %)

Reaction of 3a with chloroacetic acid. Formation of 5c.

A mixture of pyridazinone (**3a**) (0.01 mol) in ethanol (50 ml) was treated with aqueous 20% NaOH solution (15 ml) and chloroacetic acid (0.01 mole) and then refluxed for 4 h, cooled then acidified by dilute HCl. The solid obtained was filtered off, washed with water several times, dried and recrystallized from benzene to give (**5c**), m.p. 240°, yield 45% (Found: C, 76.35; H, 6.52; N, 12.40; $C_{21}H_{21}N_3O$ requires: C, 76.10; H, 6.38; N, 12.67%).

Reaction (**3a**) *with $POCl_3$. Formation of* (**6**)

A mixture of (**3a**) (0.01 mol) and $POCl_3$ (20 ml) was gently refluxed for 30 minutes, cooled, treated with crushed ice and the precipitated solid filtered and crystallized from benzene to give (**6**), m.p. 130°C; yield 43% (Found: C, 71.83; H, 4.86; N, 12.71 $C_{20}H_{16}ClN_3$ requires: C, 71.95; H, 4.83; N, 12.58%).

Reaction of (**6**) *with anthranilic acid: Formation of* (**8**)

A mixture of (**6**) (0.01 mol) and anthranilic acid (0.02 mol) was heated in an oil bath at 150°C for 1 h, cooled and triturated with ethanol. The solid obtained was crystallized from ethanol to give (**8**), m.p. 195°C; yield 70% (Found: C, 77.59; H, 5.10; N, 13.62 $C_{27}H_{20}N_4O$ requires: C, 77.86; H, 4.84; N, 13.45%).

Reaction of (**6**) *with sodium azide. Formation of* (**9**).

A mixture of (**6**) (1 g), sodium azide (2 g) water (5 ml), and N,N-dimethylformamide (20 ml) was boiled for 2 h and then cooled. The solid obtained upon dilution with water was filtered and crystallized from ethanol to give (**5**), m.p. 170°C, yield 43% (Found: C, 70.82; H, 4.85; N, 24.30 $C_{20}H_{16}N_6$ requires: C, 70.57; H, 4.73; N, 24.69%).

Reaction of (**3a**) *with P_2S_5. Formation of* (**10a**)

A solution of (**3a**) (0.01 mol), P_2S_5 (0.03 mol) and dry xylene (50 ml) was boiled under reflux for 6 h. The reaction mixture was filtered while hot and then concentrated. The product which separated on cooling was crystallized from ethanol to give (**10a**), m.p. 150°C yield 60% (Found: C, 72.50; H, 5.35; N, 12.50 $C_{20}H_{17}N_3S$ requires: C, 72.47; H, 5.17; N, 12.67%).

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