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Synthesis and Biological Effects of 2,3-Diphenyl-5-Methoxyindole and Substituted Benzophenone Derivatives

O.H. Hishmat, O.A. El-Shabrawy*, S.S. Nakkady and S.S. Mahmoud*

*Natural Products Department and *Pharmacology Department*
National Research Centre, Dokki, Cairo
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Abstract □ Seven 2,3-diphenyl-5-methoxyindole derivatives were synthesized. The effect of structural variation of these molecules on biological activities was examined. None of the tested compounds was found to be toxic up to 5 gm/Kg body weight. Four compounds demonstrated smooth muscle relaxant effects and one showed a persistent hypotensive effect. Only the parent compound, 2,3-diphenyl-5-methoxyindole, showed a significant analgesic effect.

Keywords □ 2,3-Diphenyl-5-methoxyindole derivatives, substituted benzophenones, toxicity, smooth muscle relaxant effect, hypotensive, analgesic activity.

It is well known that indole derivatives possess pronounced biological properties, *i.e.* hypotensive[1], anti-inflammatory[2,3] activities, *etc.* Therefore it became of interest to synthesize some new indole derivatives in order to test their toxic and pharmacological effects.

Chemistry

2,3-Diphenyl-5-methoxyindole **(I)**[4] was prepared by fusion of benzoin and *p*-anisidine hydrochloride.

Friedel-Craft acetylation of I using acetyl chloride and anhydrous aluminium chloride in benzene or nitrobenzene gave the 6-acetyl derivative **(II)**.

6-Acetyl-2,3-diphenyl-5-methoxyindole **(II)** forms chalkones **(IIIa-c)** by the condensation of aromatic aldehydes, *i.e.* benzaldehyde, anisaldehyde, anisaldehyde and 4-methoxybenzaldehyde in the presence of sodium hydroxide solution.

2,3-Diphenyl-5-methoxyindole **(I)** reacts readily with bromine in acetic acid to yield 4,6-dibromo-5-methoxy-2-(p-bromophenyl)-3-phenylindole**(IV)**.

Oxidation of IV using chromium trioxide and acetic acid gave 2-(p-bromobenzamido)-4,6-dibromo-5-methoxybenzophenone **(V)**.

Hydrolysis of **(V)** using sulphuric-acetic acid mixture led to the formation of 2-amino-4,6-dibromo-5-methoxybenzophenone **(VI)**, thus proving that bromination occurred at the phenyl group attached to C_2 in the original indole **(I)**.

Biology

Acute oral and intraperitoneal administration of the tested compounds up to 5 gm/Kg body weight to rats and mice failed to produce any lethal effect within the first twenty four hours after administration. With the exception of the drowsiness and the sluggish movements observed in some high doses in both rats and mice, no other toxic symptoms were observed as a result of treatment with the tested compounds.

The nontoxic effect demonstrated by these compounds was found to be in agreement with the results previously reported[5] as they were able to demonstrate nontoxic effect of the derivatives of 5-hydroxy and 5-methoxy-indole with various substituents in 1,2,3-positions of the indole ring.

Compounds **I, II, IV** and **V** were found to have a smooth muscle relaxant effect with variation in their potency, Others, **IIIa-IIIb** and **VI** were not able to demonstrate any smooth muscle relaxant effect. Table I showed the effect of the tested compounds with smooth muscle relaxant effect. The site of action of the tested compounds was found to have a direct effect on the intestinal muscles, as the tested compounds were able to produce smooth muscle relaxant effect after complete nicotinisation, atropinisation, barium chloride and acetyl coline induced spasms.

It was noticed that the most active compound was the parent compound "2,3-diphenyl-5-me-

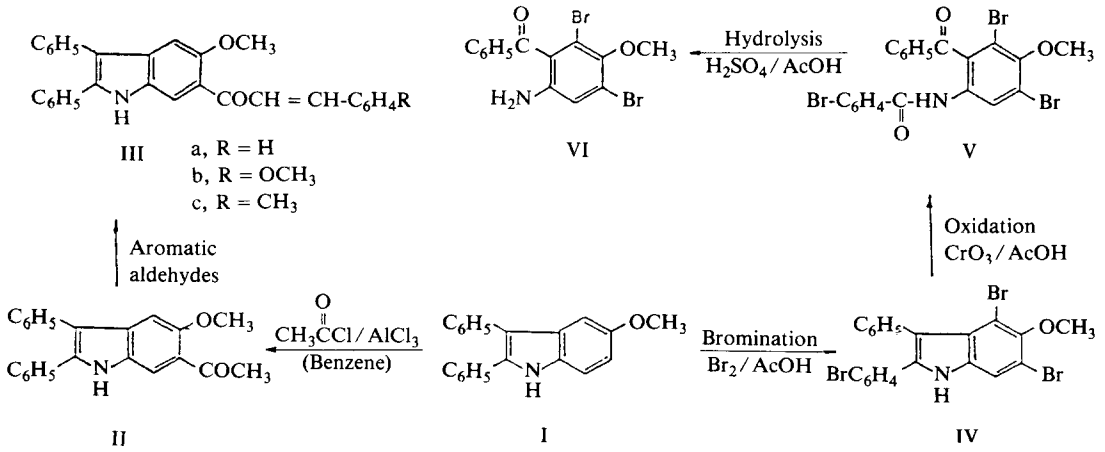

Table I. Effect of the compounds on the smooth muscle of the isolated rabbit intestine.

Compounds	ED_{50} and its confidence limits(mg/50 ml/ bath)
I	23(10.45 to 50.6)
II	115(74.19 to 178.25)
IV	119(54.09 to 261.8)
V	98(63.23 to 151.9)

thoxyindole" **(I)**, while substitution at the 6-position by an acetyl group as in **II** decreased the smooth muscle relaxant action as indicated by increased ED 50 values. Bromination of I decreased the activity as in IV while oxidation of the latter compound to give the benzophenone derivative **(V)** increased the effect slightly.

Compounds **IIIb, V** and **VI** showed temporary hypotensive effect that returns back to normal after a short period of time depending on the dose used, while other compounds failed to demonstrate any hypotensive effect. Compound **V** was found to be the most effective and produce persistent hypotensive effect. The different compounds affected the respiration slightly, compound **V** produced a decrease in the depth and rate of respiration (Fig. 1).

It is of interest to note that oxidation to the benzophenone derivative **(V)** not only increased the smooth muscle effect but also prolonged the hypotensive activity.

On studying the analgesic effect of the tested compounds it was found that, the parent compound I showed a significant analgesic effect, while the 150 mg/100 gm body weight (Table II).

EXPERIMENTAL

Melting points are not corrected. The infra red spectra were carried out in potassium bromide on a Unicam Sp 2000 spectrophotometer. The ^1H MMR spectra (at 100 MHz) on a FT 100, FA Jeal, Tokyo, using TMS as internal standard, and $CDCl_3$ as solvent. The mass spectra were run on a Varian Mat CH-4B spectrometer.

1) Preparation of 2,3-diphenyl-5-methoxyindole (I)

P-anisidine hydrochloride 4.5 g was added to 6.3 g of benzoin. The reaction mixture was heated to

Table II. Analgesic effect of the compounds in mice

Treatment Dose mg/100B.wt	Time in minutes ± S.E.					
	10	20	30	45	60	120
Control	15.83 ± 0.48	18 ± 0.58	18 ± 0.60	17.8 ± 0.49	17.33 ± 0.59	16 ± 0.59
Paracetamol (50)	18.17 ± 1.2	26.5** ± 2.1	23.5** ± 0.96	24.33** ± 1.33	23.66** ± 0.67	20.67** ± 0.88
I (50)	16 ± 0.36	21.33** ± 0.66	20.83 ± 0.6	21** ± 0.58	17.5 ± 0.43	16.5 ± 0.62

** significant at $p<0.01$.
* significant at $p<0.05$.

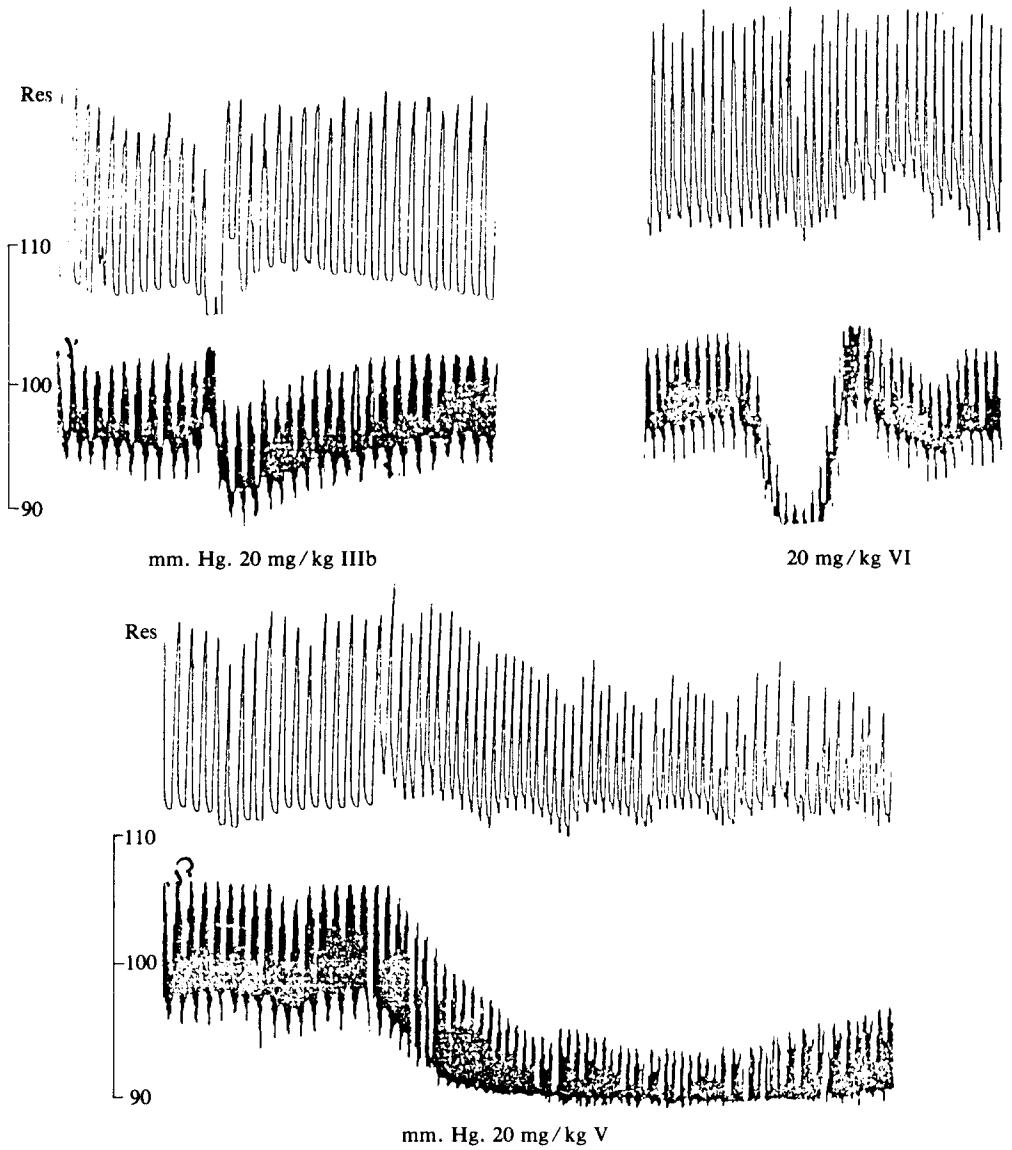

Fig. 1. Effect of compounds (IIIb, VI, V) on the arterial blood pressure and respiration of anaesthetized dogs.

200 °C in an oil bath for 15 minutes till complete elimination of water. Three drops of concentrated hydrochloric acid were added while stirring, the mixture was cooled and digested with methanol, filtered and crystallized from methanol as yellowish crystals, m.p. 145 °C yield Ca 80%. Calcd for $C_{21}H_{17}NO$, C: 84.28, H: 5.68, N: 4.68. Found C: 83.87, H: 5.59, N: 4.35%. ^{1}H-NMR: δ 8.15 (1H, NH, broad *s*), δ 7.3-7.5(10H, aromatic protons, *m*), δ 7.2(1H, H_{-4}, *s*), δ 6.95 and 6.8 (1H, each, H_{-6} and H_{-7}, *d*) and 3.85 (3H, OCH_3, *s*).

2) Preparation of 6-acetyl-2,3-diphenyl-5-methoxyindole (II)

To a mixture of I (1g) and anhydrous aluminium chloride (3g) in dry benzene (20 m*l*), acetyl chloride (3 m*l*) was slowly added dropwise (20 minutes) with shaking till all the hydrochloric acid gas evelved. The reaction mixture was poured on to acidified ice, extracted with benzene and the solvent evaporated. The solid so obtained was crystallized from chloroform as greenish white crystals, m.p. 290 °C, yield Ca 70%. Calcd for $C_{23}H_{19}NO_2$, C: 80.93, H:

5.57, N: 4.11, Found C: 80.7, H: 5.4, N: 3.97%. IR: 3320 cm^{-1} (NH) and 1680 cm^{-1} (C = O). Mass: Molecular ion *m/e* 341 as base peak.

3) Preparation of 6-cinnamoyl-2,3-diphenyl-5-methoxyindole derivatives IIIa-c

To the solution of II in ethanol, was added 10 ml of sodium hydroxide solution (10%) followed by 1 g of the appropriate aldehyde. The reaction mixture was shaken vigorously for two hours then left at room temperature for 48 hours. It was then neutralized with dilute hydrochloric acid, filtered, washed with water and dried. The solid so obtained was crystallized from chloroform.

6-Cinnamoyl-2,3-diphenyl-5-methoxyindole (**IIIa**) was obtained as brownish crystals, m.p. 240 °C, yield Ca. 60%. Calcd. for $C_{30}H_{23}NO_2$, C: 83.9, H: 5.36, N: 3.26, Found C: 83.56, H: 5.25, N: 3.28%. IR: 3325 cm^{-1} (NH), 1660 cm^{-1} (C = O). ^{1}H-NMR: δ 8.5 (1H, C_4, s), δ 8.3 (1H, NH, broad s), δ 7.2-7.8 (16H, phenyl protons + C_7), δ 7.5 and 7.7 (2H, olefinic protons, 2d, J = 16 Hz), δ 3.9 (3H, OCH_3, s).

6-(p-Methoxycinnamoyl)-2,3-diphenyl-5-methoxyindole (**IIIb**) was prepared in 64% yield as greyish crystals, m.p. 290 °C. Calcd. for $C_{31}H_{25}NO_3$, C: 81.04, H: 5.44, N: 3.05, Found C: 80.82, H: 5.52, N: 3.23%. IR: 3250 cm^{-1} (NH), 1660 cm^{-1} (C = O).

6-(p-Methylcinnamoyl)-2,3-diphenyl-5-methoxyindole (**IIIc**) was obtained in 60% yield as yellowish crystals, m.p. 290 °C. Calcd. for $C_{31}H_{25}NO_2$, C: 83.97, H: 5.64, N: 3.16, Found, C: 83.73, H: 5.82, N: 2.93%. IR: 3310 cm^{-1} (NH), 1660 cm^{-1} (C = O).

4) Preparation of 4,6-dibromo-5-methoxy-2-(p-bromophenyl)-3-phenylindole IV

To a mixture of (2g) of I dissolved in 18 ml of glacial acetic acid was added 2.2 ml of bromine in 70 ml of glacial acetic acid. The reaction mixture was well stirred for half an hour, filtered and crystallized from ethanol as greenish white crystals of **IV**, m.p. 230 °C, yield Ca. 70%. Calcd. for $C_{21}H_{14}NOBr_3$, C: 47.01, H: 2.61, Found C: 47.26, H: 2.81, N: 2.36%. IR: 3300 cm^{-1} (NH), 690 cm^{-1} (C-Br). ^{1}H NMR: 11.5 (1H, NH, broad s, disappears with D_2O), δ 7.8 (2H, H_2' and H_6', d), δ 7.2-7.6 (5H, phenyl protons, m), δ 7.0 (2H, H_3' and H_5', d), δ 6.9 (1H, H_7, s) and δ 3.8(3H, OCH_3, s). Mass: Molecular ion *m/e* 536 as base peak.

5) Preparation of 2-(p-bromobenzamido)-4,6-dibromo-5-methoxy-benzophenone V

A mixture of IV (1g) in 20 ml glacial acetic acid was refluxed on a sand bath for half an hour, poured on cold water then left to cool, filtered and crystallized from chloroform as white crystals of **V**, m.p. 195 °C. (decomposition followed by sublimation), yield Ca. 70%. Calcd. for $C_{21}H_{14}NO_3Br_3$, C: 44.36, H: 2.46, Found C: 44.01, H: 2.69, N: 2.18%. IR: 1655 cm^{-1} (amide I), 1675 cm^{-1} (Ar-C-Ar). ^{1}H NMR: δ 9.1 (1H, NH, broad s), δ 8.2 (1H, H_3, s), δ 7.8 (2H, H_2' and H_6', d), δ 7.4-7.6 (5H, phenyl protons, m), δ 7.0 (2H, H_3' and H_5', d) and δ 3.9 (3H, OCH_3, s).

6) Preparation of 2-amino-4,6-dibromo-5-methoxybenzophenone VI

Reflux (0.38 g) of V in a mixture of water: concentrated sulphuric acid: acetic acid (1:1:1)(12 ml) for two hours and then the solution was poured on to ice, the solid so obtained was filtered, dried and crystallized from petreleum ether (b.p. 80-110 °C.) as yellowish crystals of **VI**, m.p. 130 °C. yield Ca. 60%. Calcd. for $C_{14}H_{11}NO_2Br_2$, C: 43.64, H: 2.86, N: 3.64, Found, C: 43.3, H: 2.59, N: 3.36%. IR: 3320 cm^{-1} (NH_2), 1680 cm^{-1} (Ar-C-Ar), 690 cm^{-1} (C-Br).

Acute toxicity

The acute toxic effects of the synthesized compounds **I, II, IIIa, IIIb, IV, V** and **VI** were investigated using adult rats and mice. Animals were divided into groups of six animals each. The compounds were orally and intraperitoneally administered to the animals, the mortality rate, any toxic symptoms and post mortem examinations of dead animals were all observed and calculated within the first twently four hours after injection or administration. Results were recorded and statistically assessed.

Effect on smooth muscles

This effect was investigated according to the method described by Magnus[6]. Isolated perfused pieces from freshly killed rabbits were suspended in the organ bath containing Tyrod's solution heated up to 37 °C and aerated with oxygen and carbon dioxide. Different doses of the tested compounds were added to the bath after recording the normal rythmic contractions of the intestine. Each dose was tested three to four times using different pieces and the mean percentage to the method of Litchfield and Wilcoxon[7]. The site of action of the tested compounds was identified.

Effect on arterial blood pressure and respiration in dogs

Adult mongrel dogs 8-15 kg weight of either sex anaesthetized by pentobarbital sodium 30 mg/kg body weight i.v. Ghosh[8]. One common carotid artery and femoral vein were canulated using special canulas. The carotid artery was connected to a pressure tranceducer, which was connected to a Harvard 2120 biograph recorder. Respiration was recorded by inserting special electrodes to the chest wall and abdomen, which were connected to the same recorder. Tested compounds dissolved in 50% propylene glycol in distilled water were injected into the femoral vein and washed in with 0.5 m*l* saline. Each dose was tested 2-4 times.

Analgesic activity

The analgesic activity of the synthesized compounds was tested using the hot plate method as described by Jansean and Jageneau[9]. The reaction time was measured by the nearest fifth of a second at 10, 20, 30, 45, 60 and 120 minutes after drug administration.

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