

O. H. Hishmat*, A. H. Abd el Rahman (1) and M. I. Moawad

National Research Centre, Dokki, Cairo, Egypt

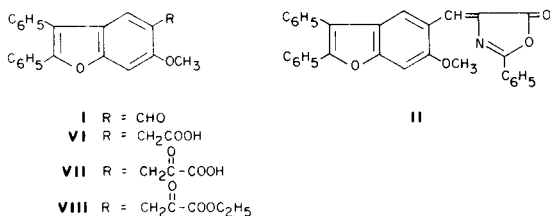
Received January 23, 1981

2,3-Diphenyl-5-formyl-6-methoxybenzofuran was reacted with hippuric acid to give 4-[(2',3'-diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-2-phenyloxazolin-5-one. The above mentioned oxazolone yielded 2,3-diphenyl-6-methoxybenzofuranylacetic acid by reaction with hydrazine hydrate, nitrous acid, benzene followed by acid hydrolysis. The reactions of the oxazolone with hydroxylamine hydrochloride and primary or secondary amines were also investigated.

J. Heterocyclic Chem., **18**, 1209 (1981).

In view of the marked biological activity of benzofuran derivatives (2-6), the present investigation has been undertaken to synthesize new derivatives for pharmacological evaluation.

For this purpose 4-[(2',3'-diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-2-phenyloxazolin-5-one (II) was prepared by condensation of 2,3-diphenyl-5-formyl-6-methoxybenzofuran (I) (7) with hippuric acid in the presence of acetic anhydride and sodium acetate.

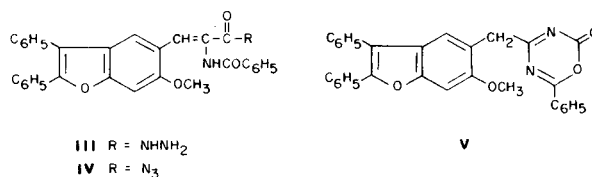


The structure of II was confirmed by the pmr spectrum which revealed the presence of singlets at δ 3.93 (3H, OCH₃), 7.15 (1H, olefinic), 8.00 (1H, C-4'), and 9.45 (H, C-7'). The spectrum showed also 15 aromatic protons as a multiplet at δ 7.20-7.65.

The ir spectrum of II showed bands at 1645 and 1760 cm⁻¹ characteristic of the C=N and C=O moieties of oxazolone ring (8), respectively.

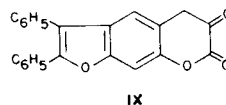
The ms of II revealed a molecular ion M⁺ at m/e 471 as the base peak.

Compound II reacted with hydrazine hydrate to give α -benzoamido- β -(2,3-diphenyl-6-methoxy-5-benzofuranyl)-acrylohydrazide (III), which when treated with nitrous acid, formed α -benzamido- β -(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylazide (IV). Compound IV upon refluxing with dry benzene decomposed with evolution of nitrogen to form 4-[(2',3'-diphenyl-6'-methoxy-5'-benzofuranyl)methyl]-6-phenyl-2H-oxadiazin-2-one (V). Hydrolysis of V with hydrochloric acid led to the formation of 2,3-diphenyl-6-methoxy-5-benzofuranylacetic acid (VI).



The pmr spectrum of III showed the protons on C-4 and C-7 of the benzofuran moiety as singlets at δ 7.90 and 8.97, (one proton for each), respectively. The spectrum also revealed singlets at δ 3.93 (3H; OCH₃) and 7.07 (1H, olefinic). Fifteen aromatic protons appeared as a multiplet at δ 7.20-7.80. The ir spectrum of III showed an absorption at 1730 cm⁻¹ due to the hydrazide group.

Alkaline hydrolysis of II with sodium hydroxide gave 2,3-diphenyl-6-methoxy-5-benzofuranylpyruvic acid (VII) which was recovered unchanged upon oxidation with hydrogen peroxide. The ethyl ester of benzofuranpyruvic acid (VIII) upon fusion with pyridine hydrochloride led to the formation of the corresponding lactone of benzofuranpyruvic acid (IX), the reaction involved demethylation followed by cyclodehydration.



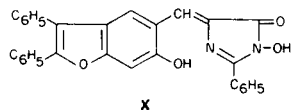
Hydroxylamine hydrochloride reacted with compound II to yield 4-[(2',3'-diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-1-hydroxy-2-phenyl-5H-imidazolin-5-one (X).

The structure of X was confirmed by the following data: a) good elemental analysis; b) compound X gave a red colour with ferric chloride solution; c) the pmr spectrum of X showed the absence of methoxy protons and the following signals appeared at δ 7.82 (s, 1H, C-4'), 8.89 (s, 1H, C-7') and 7.20-7.64 (m, 15H, aromatic); d) the ir spectrum showed bands at 1640 and 1770 cm⁻¹ corresponding to the C=N moiety of the imidazolone ring and the OH groups appeared as a broad band at 3200-3400 cm⁻¹; e) the mass spectrum revealed a molecular ion M⁺ at m/e 472.

Table 1
Physical Constants of Xa-g and XXa-b

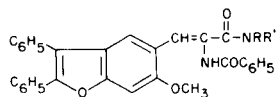
Compound	Mp °C (Solvent of Crystallization)	Yield %	Formula (Mol. Wt.)	Calcd. Found C	Analysis	
					H	N
XIa	254-256 (Acetone)	73	C ₃₂ H ₂₆ N ₂ O ₄ (502)	76.49 76.20	5.18 5.10	5.58 5.48
XIb	248-250 (Acetic acid)	90	C ₃₇ H ₂₈ N ₂ O ₄ (564)	78.72 78.40	4.96 5.02	4.96 4.57
XIc	233-235 (Acetic acid)	85	C ₃₇ H ₂₇ ClN ₂ O ₄ (598.5)	74.19 74.32	4.41 4.37	4.68 4.75
XId	242-244 (Acetic acid)	88	C ₃₇ H ₂₇ ClN ₂ O ₄ (598.5)	74.19 74.11	4.51 4.71	4.68 4.74
XIe	208-210 (Acetic acid)	80	C ₃₅ H ₃₂ N ₂ O ₄ (544)	77.21 77.01	5.88 5.95	5.15 5.50
XIf	140-142 (Methanol)	90	C ₃₅ H ₃₀ N ₂ O ₅ (558)	75.27 57.39	5.38 5.51	5.02 4.90
XIg	210-212 (Methanol)	85	C ₃₆ H ₃₂ N ₂ O ₄ (556)	77.70 77.52	5.76 6.03	5.03 5.95
XIh	226-228 (Acetone)	70	C ₃₇ H ₂₉ N ₃ O ₄ (579)	76.68 76.39	5.01 5.00	7.25 7.53
XXa	212-214 (Benzene)	76	C ₃₇ H ₂₈ N ₂ O ₄ (564)	78.72 78.39	4.96 4.63	4.96 4.54
XXb	224-226 (Methanol)	70	C ₃₈ H ₃₀ N ₂ O ₄ (578)	78.89 78.72	5.19 5.45	4.84 4.61

The demethylation by hydroxylamine hydrochloride was similar to the facile demethylation occurring under the influence of aniline hydrochloride (9), pyridine hydrochloride (10) or of magnesium iodide (11).



X

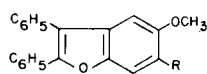
The oxazolone II reacted with methylamine, aniline, *m*-chloroaniline, *p*-chloroaniline, diethylamine, morpholine, piperidine and phenylhydrazine to give the corresponding acrylamide derivatives XIa-h.



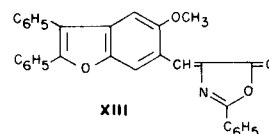
- XI
- a R = H, R' = CH₃
 - b R = H, R' = C₂H₅
 - c R = H, R' = C₆H₄Cl-*m*
 - d R = H, R' = C₆H₄Cl-*p*
 - e R = R' = C₂H₅
 - f NRR' = morpholino
 - g NRR' = piperidino
 - h RR' = NHC₆H₅

formyl-5-methoxybenzofuran (XII) (7) by conversion of oxazolone XIII, which with hydrazine hydrate yielded the hydrazide XIV. The hydrazide XIV gave the azide XV. The azide XV on heating with benzene furnished the oxadiazine XVI, furnishing XVII on hydrolysis.

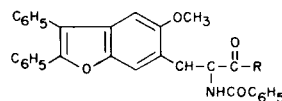
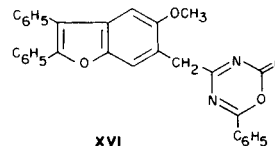
Alkaline hydrolysis of oxazolone XIII with sodium hydroxide gave the pyruvic acid derivative XVIII.



XII R = CHO

XVII R = CH₂COOHXVIII R = CH₂COCOOH

XIII

XIV R = NHHNH₂XV R = N₃

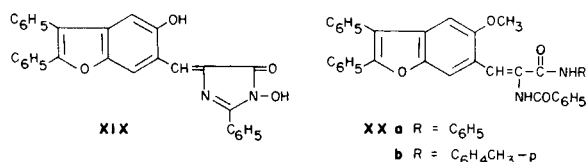
XVI

4-[(2',3'-Diphenyl-5'-methoxy-6'-benzofuranyl)methylene]-2-phenyloxazolin-5-one (XIII) was reacted with hydroxylamine hydrochloride to give the corresponding imidazole XIX.

The acrylamides XXa and b were formed by action of aniline and *p*-toluidine on compound XIII.

The ir spectra of IIa,b,e and f showed C=O bands at 1660-1670 cm⁻¹ and 3080-3100 cm⁻¹ (>NH). The ms of IIe showed a molecular ion M⁺ at m/e 544.

In this investigation 2,3-diphenyl-5-methoxy-6-benzofuranylacetic acid (XVII) was formed from 2,3-diphenyl-6-



EXPERIMENTAL

All melting points are uncorrected. The infrared spectra were recorded on a Carl-Zeise Infra-Red Spectrophotometer Model "UR-10" in potassium bromide. The pmr spectra were carried out in deuteriochloroform at 60 MHz with TMS as the internal standard on a Varian instrument. Mass Spectra were run at 70 ev on Varian Mat 112 Spectrometer.

4-[2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-2-phenyloxazolin-5-one (II).

A mixture of 2,3-diphenyl-5-formyl-6-methoxybenzofuran (I) (4 g), hippuric acid (8 g), and anhydrous sodium acetate (4 g) in 25 ml of acetic anhydride was heated on a water bath for 2 hours and kept overnight. The crystalline solid was filtered and recrystallized from chloroform as yellow needles. The yield obtained was 60% and the mp was 262-264°.

Anal. Calcd. for $\text{C}_{31}\text{H}_{21}\text{NO}_4$ (471): C, 78.98; H, 4.46; N, 2.97. Found: C, 79.12; H, 4.32; N, 2.69.

α -Benzamido- β -(2,3-diphenyl-6-methoxy-5-benzofuranyl)acrylhydrazone (III).

To a suspension of finely powdered oxazolone (II) (5 g) in chloroform (150 ml), hydrazine hydrate (98%, 5 ml) was added. The mixture was refluxed for 3 hours, and allowed to cool. The solid so obtained was crystallized from acetone to give the acrylhydrazone III (90%) as yellow crystals, mp 231-233°.

Anal. Calcd. for $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_4$ (503): C, 73.96; H, 4.97; N, 8.35. Found: C, 73.90; H, 5.20; N, 8.12.

4-[(2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methyl]-6-phenyl-2H-1,3,5-oxadiazin-2-one (V).

An ice-cold solution of sodium nitrite (0.3 g) in a minimum amount of water was added slowly to a solution of III (1 g) in acetic acid (25 ml), the temperature was kept below 5°. After 30 minutes stirring, the yellow crystals of the azide IV was formed, filtered, washed with water and dried, mp 215° dec.

The crude azide IV was extracted from soxhlet-thimble with boiling benzene (50 ml), then concentrated and cooled, the benzene extract deposited a product which on crystallization from benzene gave V as yellow crystals, mp 207-209°, yield 60%.

Anal. Calcd. for $\text{C}_{31}\text{H}_{23}\text{N}_3\text{O}_4$ (486): C, 76.54; H, 4.53; N, 5.76. Found: C, 76.29; H, 4.50; N, 5.62.

2,3-Diphenyl-6-methoxy-5-benzofuranylacetic Acid (VI).

A suspension of the above-mentioned oxadiazine V (3.5 g) in acetic acid (40 ml) and 5N hydrochloric acid (5 ml) was refluxed until it dissolved completely and the color of the solution was completely discharged. The reaction mixture was diluted with water (40 ml) to give VI and benzoic acid. The latter was leached out with water at 60° leaving the crude VI which was crystallized from ethanol as colourless crystals, mp 164-166°, (yield 70%).

Anal. Calcd. for $\text{C}_{25}\text{H}_{19}\text{O}_4$ (358): C, 77.09; H, 5.03. Found: C, 77.10; H, 5.10.

2,3-Diphenyl-6-methoxy-5-benzofuranylpyruvic Acid (VII).

The oxazolone II (1 g) was boiled gently under reflux with 20% solution of sodium hydroxide (20 ml) until the solution became clear. The condenser was then removed and hydrolysis was completed by gentle

boiling until free of ammonia. During the later part of the reaction, the volume of the solution was kept at 20 ml by occasional addition of water. The solution was diluted with water (50 ml) and filtered. The cold filtrate was acidified with hydrochloric acid and warmed on a steam bath to 60°. In this form the pyruvic acid separated in granular form and was easily filtered. The benzoic acid formed in the reaction remained in solution. The pyruvic acid separated and crystallized from aqueous ethanol (1:1) as colourless crystals, mp 267-269°, yield 60%.

Anal. Calcd. for $\text{C}_{24}\text{H}_{18}\text{O}_5$ (386): C, 74.61; H, 4.66. Found: C, 74.30; H, 4.40.

The ethyl ester VIII of the above mentioned pyruvic acid was prepared as colourless needles mp 180-182°, yield 85%.

Anal. Calcd. for $\text{C}_{26}\text{H}_{22}\text{O}_5$ (414): C, 75.36; H, 5.31. Found: C, 75.60; H, 4.99.

Action of Pyridine Hydrochloride on Compound VIII.

A mixture of VIII (1 g) and freshly prepared pyridine hydrochloride (3 g) was refluxed for 30 minutes, then allowed to cool and acidified with dilute hydrochloric acid. The solid that separated was crystallized from ethanol as white crystals, mp 93-95°, yield 25%.

Anal. Calcd. for $\text{C}_{23}\text{H}_{14}\text{O}_4$ (354): C, 77.97; H, 3.95. Found: C, 78.23; H, 4.21.

4-[(2',3'-Diphenyl-6'-methoxy-5'-benzofuranyl)methylene]-1-hydroxy-2-phenyl-5H-imidazolin-5-one (X).

To a solution of oxazolone II (1 g) in ethanol (50 ml) hydroxylamine hydrochloride (1 g) was added. The reaction mixture was refluxed for 5 hours and allowed to cool. The solid so obtained was crystallized from ethanol as yellow crystals, mp 234-236°, yield 65%.

Anal. Calcd. for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_4$ (472): C, 76.27; H, 4.24; N, 5.93. Found: C, 76.40; H, 4.40; N, 6.01.

Preparation of α -Benzamidoacrylamides Derivatives (XIa-g and XXa-b).

General Procedure:

A mixture of 0.01 mole of II or X and 0.03 mole of the appropriate amine in 30 ml of ethanol was refluxed for 5 hours, then concentrated to about 10 ml. The solid so obtained was collected and crystallized from a suitable solvent to give the acrylamides XIa-g and XXa-b (see Table 1).

4-[(2',3'-Diphenyl-5'-methoxy-6'-benzofuranyl)methylene]-2-phenyloxazolin-5-one (XII).

A mixture of 2,3-diphenyl-6-formyl-5-methoxybenzofuran (XII) (4 g), hippuric acid (7 g) and anhydrous sodium acetate (4 g) in 25 ml of acetic anhydride gave XIII as yellow crystals, mp 255-257°, yield 80%.

Anal. Calcd. for $\text{C}_{31}\text{H}_{21}\text{NO}_4$ (471): C, 78.98; H, 4.46; N, 2.97. Found: C, 78.66; H, 4.68; N, 3.01.

α -Benzamido- β -(diphenyl-5-methoxy-6-benzofuranyl)acrylhydrazone (XIV).

A mixture of oxazolone XIII (5 g) and 5 ml of hydrazine hydrate gave 70% of XIV as yellow crystals, mp 252-254°.

Anal. Calcd. for $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_4$ (503): C, 73.96; H, 4.97; N, 8.35. Found: C, 73.79; H, 5.03; N, 8.69.

4-[(2',3'-Diphenyl-5'-methoxy-6'-benzofuranyl)methyl]-6-phenyl-2H-1,3,5-oxadiazin-2-one (XVI).

An ice-cold solution of sodium nitrite (0.3 g) was added to a solution of 1 g of XIV in acetic acid to give the azide XV, mp 207° dec.

The crude azide XV (1 g) was extracted with benzene to yield XVI as yellow crystals from acetone, mp 184-186°, yield 70%.

Anal. Calcd. for $\text{C}_{31}\text{H}_{23}\text{N}_3\text{O}_4$ (486): C, 76.54; H, 4.53; N, 5.76. Found: C, 76.35; H, 4.29; N, 5.47.

2,3-Diphenyl-5-methoxy-6-benzofuranylacetic Acid (XVII).

Hydrolysis of oxadiazone XVI (3.5 g) with 5N hydrochloric acid gave XVII as yellow crystals (benzene), mp 140-142°, yield 70%.

Anal. Calcd. for $C_{23}H_{18}O_4$ (358): C, 77.09; H, 5.03. Found: C, 77.21; H, 4.94.

2,3-Diphenyl-5-methoxy-6-benzofuranylpyruvic Acid (XVIII).

A mixture of XIII (1 g) and sodium hydroxide (10%, 20 ml) furnished XVIII as colourless crystals from benzene, mp 215-217°, yield 70%.

Anal. Calcd. for $C_{24}H_{18}O_5$ (386): C, 74.61; H, 4.66. Found: C, 74.64; H, 4.75.

The ethyl ester of the above mentioned pyruvic acid was prepared as colourless crystals, mp 90-92° from petroleum-ether, bp 60-80°.

Anal. Calcd. for $C_{26}H_{22}O_5$ (414): C, 75.36; H, 5.31. Found: C, 74.98; H, 5.66.

4-[(2',3'-Diphenyl-5'-methoxy-6'-benzofuranyl)methylene]-1-hydroxy-2-phenyl-5H-imidazolin-5-one (XIX).

A mixture of oxazolone XIII (1 g) and hydroxylamine hydrochloride (1 g) gave XIX as yellow crystals (benzene), mp 230°, yield 80%.

Anal. Calcd. for $C_{30}H_{20}N_2O_4$ (472): C, 76.27; H, 4.24; N, 5.93. Found: C, 75.99. H, 4.58; N, 6.05.

REFERENCES AND NOTES

- (1) Department of Chemistry, Mansoura University.
- (2) R. Royer, L. Rene, P. Demerseman, R. Cavier and J. Canac, *Eur. J. Med. Chem., Chim. Ther.*, **6**, 97 (1971).
- (3) A. H. Abd el Rahman and E. M. Ismail, *Arzneim-Forsch.*, **26**, 756 (1976).
- (4) G. Raymond, M. Thomas and J. Thomas, *Eur. J. Med. Chem., Chim. Ther.*, **8**, 479 (1973).
- (5) G. Raymond, B. Pourrias, M. Thomas and J. Thomas, *ibid.*, **9**, 85 (1974).
- (6) A. E. Lipken, I. S. Chichkanova and T. A. Degtyareva, *Khim.-Farm. Zh.* **9**, 18 (1970); *Chem. Abstr.*, **74**, 12725 (1971).
- (7) O. H. Hishmat and A. H. Abd el Rahman, *Aust. J. Chem.*, **27**, 2499 (1974).
- (8) L. J. Bellamy, "The Infra-red Spectra of Complex Molecular Molecules", Mathuen, London, 2nd Ed., 1966, p. 132.
- (9) A. Schonberg and J. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953).
- (10) L. Rene, J. Buisson and R. Royer, *Bull. Soc. Chim. France*, 2763 (1975).
- (11) A. Schonberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 4826 (1950).