Benzofurano Derivatives of Coumarins as Possible Antifertility Agents

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Synthesis and medicinal importance of 4-methyl-6-nitro-8,9,10,11-tetrahydro-2*H*-benzofuro[2,3-*b*]-1-benzopyran-2-one (I), 4-ethyl-11-nitro-6,7,8,9-tetrahydro-2*H*-benzofuro[3,2-*g*]-1-benzopyran-2-one (II), and 6,7-dihydro-4,13-dimethylbis-1-benzopyrano[6,7-*d*:7',6'-*d*']-2*H*,11*H*-benzo[1,2-*b*:3,4-*b*']difuran-2,11-dione (III) is presented. The structures of these compounds were confirmed by elemental analysis and spectral studies.

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Of drugs requiring a prescription, oral contraceptives are among the most widely used agents. The most common type of oral contraceptives are the combination preparation which contains both an estrogen and progesten. A variety of major and minor side-effects have been attributed to the use of steroidal antifertility agents. Of most concern are cardiovascular side-effects and the induction and promotion of tumors. The frequent mild side-effects are nausea, discomfort in the breasts, dizziness, headache, occasional vomiting and gain in weight.

Efforts were being made to synthesize non-steroidal antifertility agents with less or least side-effects and in this direction coumarin and benzofurano derivatives are well known [3-10]. In our earlier studies some cyclohexane derivatives have also shown some very promising activity [11-12]. Considering the pharmacological importance of the cyclohexane and the benzofurano systems, we combined both of the nuclii together and this class of compounds has shown anti-spermatogenic activity in gerbils (*Maeriones hurrianae* Jerdon), house rats, dogs and monkeys [13-15].

Recently Bordin *et al* have reported that some 6,7- or 7,8-furanocoumarins, which in preclinical evaluation have shown DNA synthesis inhibiting activity, mutagenic activity, skin phototoxic activity and antisporasis activity [16]. Looking into the great medical importance of these compounds we wish to report the synthesis of I, II and III. The preliminary screening of these compounds was quite encouraging (especially antifertility activity) but further studies like DNA synthesis inhibiting activity, mutagenic activity, skin phototoxic activity and antisporasis activity are in progress.

Discussion.

The ir spectra of I and II gave characteristic absorption bands at 1700 cm^{-1} indicating the presence of a C=O group in the coumarin system.

In the nmr spectra of both of the compounds there is a sharp singlet at δ 3.0 for 3 protons and at δ 7.0 for one proton accounting for one methyl group at position four and an olefinic proton at position three of the coumarin system. The singlet for the methyl group shifted from δ 2.4 to δ 3.00 and the olefinic protons from δ 6.2 to δ 7.0 thus indicating the effect of the nitro group in the system. In the aromatic region at δ 7.6 for 1-H in I and at δ 8.3 for 1-H in II indicated the presence of only one aromatic proton in I and II respectively. Hydrogen bonding of this proton with the nitro group in II shifted the signal far downfield. Eight protons for methylene groups giving signals at δ 1.8 to 2.8 appeared to have shifted downfield as compared with those of 4-methyl-11-nitro-6,7,8,9-tetrahydro-2*H*-benzofuro[3,2-*g*]-1-benzopyran-2-one (II) (1.1-2.1).

In the ir spectrum of III a strong absorption at 1700 cm^{-1} indicated the presence of the C=O group in the coumarin system. In the nmr spectrum a sharp singlet at δ

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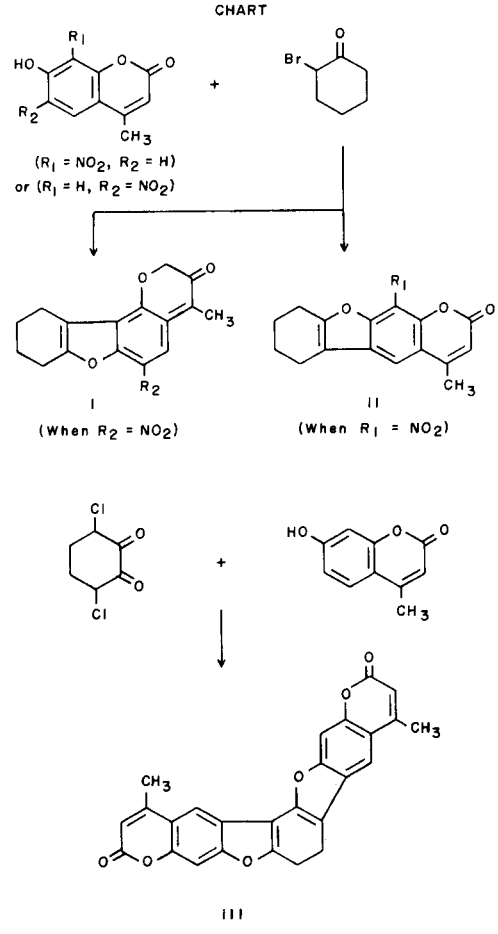

Table 1a

Physical Data and Elemental Analysis *etc*

Compound Number	Molecular Formula	Rf	Mp °C	Yield (%)	Elemental Analysis C Calcd.	C Found	H Calcd.	H Found
I	$C_{16}H_{13}O_5N$	0.63	206-207	36.05	64.21	63.98	4.34	4.12
II	$C_{16}H_{13}O_5N$	0.34	214-215	35.65	64.21	63.86	4.34	4.08
III	$C_{26}H_{16}O_6$	0.64	222-224	40.09	73.46	73.34	3.77	3.58

Table 1b

NMR Spectra (TMS as Internal Reference, Chemical Shifts Expressed in δ ppm)

Compound Number	Molecular Formula	Ar-H	=CH	-C-CH_3	-CH_2S
I	$C_{16}H_{13}O_5N$	7.60 7H	7.0 (s) 1H	3.0 (s) 3H	1.8-2.8 8H
II	$C_{16}H_{13}O_5N$	8.30 1H	7.0 1H	3.0 (s) 3H	1.8-2.8 8H
III	$C_{26}H_{16}O_6$	6.8-7.6 4H	6.15 2H	2.4 (s) 6H	1.2-2.2 4H

Solvents: TFA and deuteriochloroform.

2.4 for 6 protons, a broad singlet at δ 6.15 for two protons indicating the presence of two C-CH_3 groups and two olefinic protons separately. In the range of δ 1.1 to 2.1 there was an indication of 4 protons, which mean the involvement of two more methylene groups in the reaction. In the aromatic region (δ 6.8 to δ 7.8) there was an indication of 4-aromatic protons. Thus the presence of two C-CH_3, two olefinic and 4-aromatic protons along with the absence of 4-methylene protons indicated the participation of two coumarin systems in the reaction of 7-hydroxy-4-methylcoumarin with 3,6-dichlorocyclohexane-1,2-dione. This confirms the structure of III as 6,7-dihydro-4,13-dimethylbis-1-benzopyrano[6,7-*d*:7',6'-*d'*]-2*H*,11*H*-benzo[1,2-*b*:3,4-*b'*]difuran-2,11-dione.

Physical data and elemental analyses are given in Table 1.

EXPERIMENTAL

All melting points are uncorrected. The nmr spectra were recorded with a Perkin Elmer $R_{12}B$ spectrometer using TMS as the internal reference standard and deuteriochloroform as solvent. Purity of the compounds was ascertained by tlc using 0.25 mm thick plates coated with silica gel-G as stationary phase and benzene-methanol-ammonia (7:2:1) as mobile phase.

4-Methyl-6-nitro-8,9,10,11-tetrahydro-2*H*-benzofuro[2,3-*h*]-1-benzopyran-2-one (I).

This compound was obtained by the treatment of 2-bromocyclohexanone (3.54 g, 0.02 mole) with 7-hydroxy-4-methyl-6-nitrocoumarin (2.21 g, 0.01 mole) in dry *o*-xylene (40 ml) and potassium carbonate (8 g) at reflux temperature for 70 hours. After the usual work up the crude product was refluxed for 8 hours in aqueous potassium hydroxide (0.1 *N*). The reaction mixture was cooled and filtered, the organic phase was washed with water, dried over anhydrous sodium sulfate and the solvent rotoevaporated. The crude product was purified by column chromatography. The sticky substance so obtained was crystallised from chloroform as white needles (mp 206-207°, yield 1.07 g (36%), Rf, 0.63) (*cf*, Table 1).

Along similar lines, 4-methyl-11-nitro-6,7,8,9-tetrahydro-2*H*-benzofuro[3,2-*g*]-1-benzopyrazone (II) was synthesized in 37% yield (mp 214-215°, Rf, 0.34) (*cf*, Table 1).

6,7-Dihydro-4,13-dimethylbis-1-benzopyrano[6,7-*d*:7',6'-*d'*]-2*H*,11*H*-benzo[1,2-*b*:3,4-*b'*]difuran-2-one (III).

This compound was prepared by the condensation of 7-hydroxy-4-methylcoumarin [18] (8.80 g, 0.05 mole) with 3,6-dichlorocyclohexane-1,2-dione (3.62 g, 0.02 mole), anhydrous potassium carbonate (8 g) in dry acetone. The reaction mixture was refluxed for 72 hours (monitored by tlc). The crude product, so obtained, was refluxed for 6 hours with 0.1 *N* potassium hydroxide. After the usual work up the product was purified first by column chromatography and then by crystallisation from chloroform as a white solid in 40% yield (4.29 g) (mp 222-224°, Rf, 0.64) (*cf*, Table 1).

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