Notes

2,3-Diarylphthalimidines

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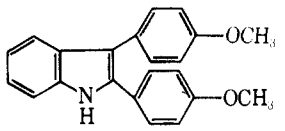
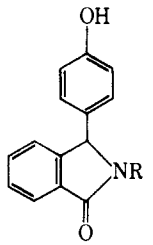
2,3-Bis(*p*-methoxyphenyl)indole (A)[1] has been of interest as an antiinflammatory agent, and a variety of



A

diarylindenes,[2] benzofurans,[3a] naphthofurans,[3b] and indoles[4] have been examined as antifertility agents. The subject of this report is the synthesis and biological evaluation of a series of 2,3-disubstituted phthalimidines related to the above structures.

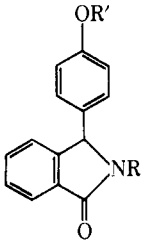
TABLE I



Compd	R	Mp, °C (recrystn solvent)[a]	% yield
2b	C_6H_5	270–274	88[b]
3	*p*-$CH_3OC_6H_4$	255–260 (C)	87
4	*p*-$CH_3C_6H_4$	273–274 (D)	90
5	*m*-$CF_3C_6H_4$	228–231 (C)	86
6	*p*-ClC_6H_4	253–257 (C)	87
7	*m*-ClC_6H_4	231–233 (A)	75.5
8	*p*-$C_2H_5OC_6H_4$	251–254 (C)	85
9	*n*-C_4H_9	198–202 (B)	52.5
10	*n*-C_6H_{13}	199–202	95
11	*n*-C_8H_{17}	169–170	84
12	C_6H_{11}	302–311 (C)	80
13	C_7H_{13}	298–299 (C)	87
14	C_8H_{15}	280–281 (C)	80

[a] A, MeOH; B, *i*-PrOH; C, HOAc; D, DMF–H_2O. [b] R. Meyer and O. Fisher, *Chem. Ber.*, **44**, 1944 (1911).

TABLE II



Compd	R	R′	Mp or bp, °C (Torr) (recrystn solvent)[a]	% yield
15	*p*-$CH_3OC_6H_4$	CH_3	129–131 (B)	79.5
16	*p*-$CH_3C_6H_4$	CH_3	129–130 (B)	87
17	*m*-ClC_6H_4	CH_3	136.5–137 (A)	38
18	*n*-C_4H_9	CH_3	185–187 (0.08)	58
19	C_7H_{13}	CH_3	101–101.5 (G)	52
20	*p*-$CH_3OC_6H_4$	*n*-C_3H_7	115.5–117.5 (B)	79
21	C_6H_5	$CH_2COOC_2H_5$	154–155 (C–G)	78
22	C_6H_5	CH_2—CH—CH_2 (O)	115–116 (C–G)	13[b]
23	C_6H_5	$CH_2CH_2N(CH_3)_2$	150–151 (B–G)	43
24	C_6H_5	CH_2CH_2N	142–143 (H–G)	66
25	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	107.5–109 (B)	21
26	*p*-$CH_3OC_6H_4$	$CH_2CH_2N(C_2H_5)_2$	86–87.5 (D–G)	47
27	C_6H_{11}	$CH_2CH_2N(C_2H_5)_2$	66–67 (G)	42
28	C_6H_{11}	CH_2CH_2N	145–147 (B–G)	30
29	C_6H_{11}	CH_2CH_2N	90–91 (G)	71
30	C_8H_{15}	CH_2CH_2N ·HCl	234–235 (E–F)	51
31	C_8H_{16}	CH_2CH_2N	101–102 (G)	54

[a] A, MeOH; B, *i*-PrOH; C, Me_2CO; D, Et_2O; E, $CHCl_3$; F, THF; G, hexane; H, PhH. [b] After chromatography on silicic acid.

Chemistry.—2,3-Diarylphthalimidines have been prepared by heating an arylamine, a 3-arylphthalide, and an acid catalyst to high temperatures for several hours.[5] Using 3-(*p*-hydroxyphenyl)phthalide (**1**), we have found that with a wide variety of aromatic amines, condensation can be effected in high yields under somewhat milder conditions by heating the phthalide and an excess of amine at *ca.* 170° for 6 hr and allowing the formed H_2O to distill. With the more nucleophilic aliphatic amines the reaction can be carried out in refluxing xylene. Using these latter conditions, no product was obtained from **1** and $PhNH_2$ after 24 hr of heating. The phthalimidines were obtained as white to blue–grey, high-melting solids by direct filtration of the cooled reaction mixture and were often of sufficient purity at this stage to give elemental analyses within acceptable limits. They were conveniently recrystallized from AcOH or EtOH (Table I).

Alkylation of the free phenols was best accomplished by means of the alkyl halide and excess K_2CO_3 or Na_2CO_3 in DMF at 100° (Table II).

(1) "Indoxole." J. Szmuszkovicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, Jr., and G. A. Youngdale, *J. Med. Chem.*, **9**, 527 (1966).

(2) D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C., Lyster, and G. W. Duncan, *ibid.*, **8**, 52 (1965).

(3) (a) S. S. Tuvari and S. C. Srivastava, *J. Indian Chem. Soc.*, **44**, 421 (1967). (b) H. P. S. Chawla, P. K. Grover, N. Anand, V. P. Kamboj, and A. B. Kar, *J. Med. Chem.*, **13**, 54 (1970).

(4) (a) J. K. Landquist and C. J. Marsden, *Chem. Ind. (London)*, 1032 (1966). (b) R. N. Iyer and R. Gopalchari, *Indian J. Chem.*, **4**, 520 (1966). (c) M. R. Bell, A. W. Zalay, R. Oesterlin, P. Schane, and G. O. Potts, *J. Med. Chem.*, **13**, 664 (1970).

(5) (a) R. Meyer, *Chem. Ber.*, **44**, 1944 (1911). (b) R. Meyer, *Monatsh. Chem.*, **28**, 1211 (1908). (c) R. Meyer and O. Fisher, *Chem. Ber.*, **44**, 1944 (1911).

Biological Data.—None of the compounds screened showed significant activity when tested orally for anti-inflammatory effects using the carrageenin-induced foot edema method in the rat.[6] All of the compounds were examined for estrogenic activity and for their effect on fertility in female rats. The effects on serum cholesterol levels in the rat were also determined; the results of active compounds are tabulated in Table III. In general, these compounds were both estrogenic and antiestrogenic, the dose of each compound producing a minimal but significant increase in the weight of the uterus also inhibiting the uterotrophic response to estradiol.

TABLE III

ESTROGENIC, ANTIESTROGENIC, ANTIFERTILITY, AND HYPOCHOLESTEREMIC ACTIVITIES

Compd	Estrogenic[a]	Antiestrogenic[b]	Anti-fertility[c]	Hypo-cholesteremic[d]
23	Inact	Inact	−	160
24	100	50	±	100
25	50	50	±	256
26	50	50	+	>256
27	50	50	+	120
28	50	50	+	>256
29	10	10	+	>256
30	50	50	+	Inact
31	10[e]	10[e]	+	>256

[a] Dose (sc mg/kg per day × 3) which produced minimal but significant increase in the wt of the uterus. [b] Dose (sc mg/kg per day × 3) which significantly inhibited the uterothrophic responsiveness to 17β-estradiol (sc, 0.002 mg/kg per day × 3). [c] Extent of effect of 50 mg/kg × 6 sc dose in preventing pregnancy; (+) completely, (±) partly, (−) ineffective. [d] ED_{33}, po mg/kg per day × 4. [e] po.

Experimental Section[7]

General syntheses for compounds in Table I and II are as follows.

2-Aryl-3-(*p*-hydroxyphenyl)phthalimidine.—A mixt of 3-(*p*-hydroxyphenyl)phthalide and 2 molar equiv of arylamine was heated in an oil bath at 170–180°. H_2O which was formed during the reaction was swept out in a slow stream of N_2. After 5–6 hr, the mixture was cooled to 90° and dild with 2–3 vol of PhMe. The resulting precipitate was filtered off and recrystd from an appropriate solvent (Table I).

2-Alkyl-3-(*p*-hydroxyphenyl)phthalimidines.—A soln of 0.1 mole of 3-(*p*-hydroxyphenyl)phthalide and 0.2 mole of aliphatic amine was refluxed in 200 ml of xylene for 18–24 hr at which time 1 equiv of H_2O had been collected in an attached trap. On cooling, the product pptd out and was collected by filtration.

Alkylation of 3-(*p*-Hydroxyphenyl)-2-(substituted)phthalimidines.—A mixt of 0.1 mole of 2-aryl(or alkyl)-3-(*p*-hydroxyphenyl)phthalimidine, 100 g of powdered, anhyd K_2CO_3, 0.11 mole of alkyl halide (or dialkylaminoalkyl halide·HCl), and 300 ml of DMF was stirred under N_2 at 100–105° (oil bath) for 18–24 hr. The cooled mixt was filtered and the filtrate was evapd *in vacuo*. The residual oil which usually solidified on cooling was purified by crystn from an appropriate solvent (Table II).

Acknowledgment.—We are grateful to Dr. A. Arnold, Dr. G. Potts, and Mr. Z. Mielens for the biological data reported.

(7) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Analytical results for C, H, and N for all compounds cited were within 0.4% of the theoretical values.

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Glutarimide Antibiotics. Analogs of Streptimidone

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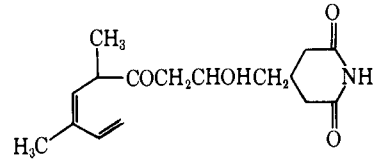
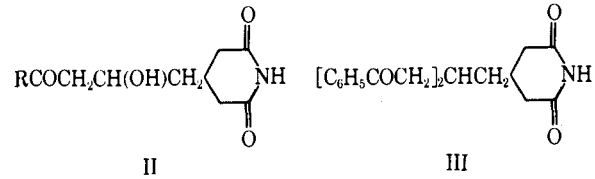
Numerous glutarimide antibiotics noted particularly for their antifungal activity have been isolated from various streptomycetes.[1] They have in common the β-(2-hydroxyethyl)glutarimide residue attached to a cyclic or acyclic ketone. Streptimidone (I) is produced[2] by *Streptomyces rimosus* forma *paramomycinus*. It is highly toxic[3] to certain species of yeast and filamentous fungi. It is effective against *Entamoeba histolytica* but not *Trichomonas vaginalis*. Toxicity against bacteria is poor; however, growth of *Brucella suis*, *Staphylococcus aureus*, and *Streptococcus pyogenes* are completely inhibited.

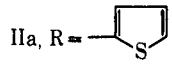


I

Analogs of I in which the 5-substituted 3-methyl-1,3-hexadiene moiety has been replaced by thiophene and benzene have been prepared.



II III



IIa, R =

IIb, R = C_6H_5

TABLE I

GLUTARIMIDE ANALOGS

Compound	% yield	Mp, °C	Formula[a]
IIa	34.0	169–170.5	$C_{13}H_{15}NO_4S$
IIb	14.3	130–132	$C_{15}H_{17}NO_4$
III	6.4	135–136.5	$C_{23}H_{23}NO_4$[b]
V	55.8	231–233	$C_{17}H_{17}N_3O_4$

[a] All compounds were analyzed for C, H, N. [b] C: calcd, 73.2; found, 74.1.

Glutarimide-β-acetaldehyde[4–6] was condensed with the Mg enolates of 2-acetylthiophene and acetophenone

(1) H. D. Sisler and M. R. Siegel, *Antibiotics*, **1**, 283.

(2) F. P. Frohardt, H. W. Dion, Z. L. Jakubowski, A. Ryder, J. C. French, and Q. R. Bartz, *J. Amer. Chem. Soc.*, **81**, 5500 (1959).

(3) D. L. Kohberger, M. W. Fisher, M. M. Galbraith, A. B. Hillegas, P. E. Thompson, and J. Ehrlich, *Antibiot. Chemother.*, **10**, 9 (1960).

(4) M. Suzuki, Y. Egawa, and T. Okuda, *Chem. Pharm. Bull.*, **11**, 589 (1963).

(5) B. C. Lawes, *J. Amer. Chem. Soc.*, **82**, 6414 (1960).

(6) F. Johnson, *J. Org. Chem.*, **27**, 3658 (1962).