

SOME OESTROGENIC 4-PHENYL-SUBSTITUTED ISOFLAV-3-ENS*

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Since certain 2- and 4-alkyl-substituted *isoflav-3-ens* have been shown to be oestrogenic (Bradbury and White 1953), it was considered of interest to prepare 4-phenyl-substituted *isoflav-3-ens*, which are structurally analogous

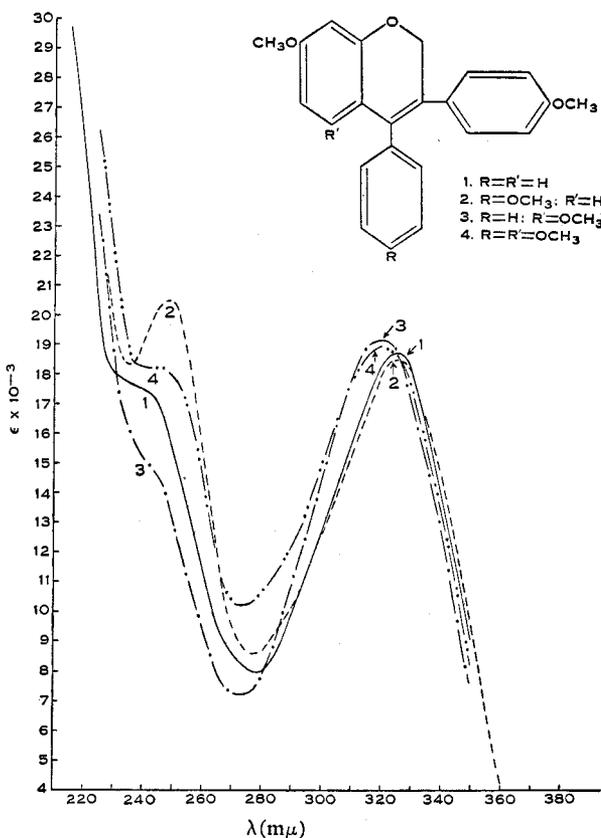


Fig. 1

prepared from 7,4'-dimethoxyisoflavanone (Anderson and Marrian 1939) and to the oestrogenic triphenylethylenes (Schonberg *et al.* 1940). 7,4'-Dimethoxy-4-phenylisoflav-3-en and 7,4'-dimethoxy-4-(*p*-methoxyphenyl)isoflav-3-en were

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the corresponding Grignard reagent, while 5,7,4'-trimethoxy-4-phenylisoflav-3-en and 5,7,4'-trimethoxy-4-(*p*-methoxyphenyl)isoflav-3-en were prepared from 5,7,4'-trimethoxyisoflavanone (Bradbury and White loc. cit.) in a similar manner.

The ultraviolet spectra of these compounds (Fig. 1) show that a *p*-methoxyl group on the 4-phenyl-substituent causes an increase in intensity of absorption at the shorter wavelength band (2400–2500 Å), but a 5-methoxyl group causes a decrease in intensity. These effects are reversed at the longer wavelength maxima, although the differences are less marked, and a distinct movement of the maxima towards shorter wavelength occurs when a 5-methoxyl group is present.

TABLE 1
OESTROGENIC ACTIVITY

Compound	Total Dose per Mouse (μg)	Average Uterine Weight*	
		Test (mg)	Control (mg)
7,4'-Dimethoxy-4-phenylisoflav-3-en ..	11.7	4.5	2.3
	23.4	7.3	"
	46.7	10.4	"
7,4' - Dimethoxy - 4 - (<i>p</i> - methoxyphenyl)isoflav-3-en	5.0	2.8	2.6
	26.0	6.8	"
	52.0	12.1	"
5,7,4'-Trimethoxy-4-phenylisoflav-3-en ..	322.0	3.2	2.4
	675.0	8.3	"
	1009.0	8.8	"
5,7,4' - Trimethoxy - 4 - (<i>p</i> - methoxyphenyl)-isoflav-3-en	442.0	4.2	2.7
	830.0	6.7	"
	1191.0	7.4	"

* Five mice.

The oestrogenic activities (Table 1) were determined by measuring the uterine weight increase in ovariectomized mice (Robinson 1949). 7,4'-Dimethoxy-4-phenylisoflav-3-en and 7,4'-dimethoxy-4-(*p*-methoxyphenyl)isoflav-3-en were both active at a total dose level of about 20 μg. A 5-methoxyl group (5,7,4'-trimethoxy-4-phenylisoflav-3-en and 5,7,4'-trimethoxy-4-(*p*-methoxyphenyl)isoflav-3-en) reduces the activity 30-fold.

7,4'-Dimethoxy-4-phenyl- and 7,4'-dimethoxy-4-(*p*-methoxyphenyl)isoflav-3-en are more active than the corresponding 4-alkylisoflav-3-ens (Bradbury and White loc. cit.), than triphenylethylene (300 μg) and triphenylchloroethylene (65 μg), and are within the range of activity of α-(4-hydroxyphenyl)stilbene (20 μg), 4,4'-dihydroxy-α-phenylstilbene (15 μg), and 4-methoxy-α-(*p*-methoxyphenyl)-β-bromostilbene (20 μg) quoted by Masson (1944).

Experimental

All melting points are corrected. The ultraviolet absorption spectra were measured in ethanol solution by means of a Beckmann DU spectrophotometer. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory.

(a) *7,4'-Dimethoxy-4-phenylisoflav-3-en.*—7,4'-Dimethoxyisoflavanone (1 g) in dry benzene (20 ml) was added to a solution of phenylmagnesium bromide prepared from bromobenzene (1.5 g) and magnesium (0.17 g) in dry ether (20 ml). After refluxing for 16 hr, 10% aqueous hydrochloric acid (100 ml) was added with shaking, and the separated benzene-ether layer washed once with water and dried over calcium chloride. The residue obtained on evaporation of the solvent was heated under reduced pressure at 250 °C for 30 min, and on crystallization from ethanol gave a yellow solid (1.2 g), which when recrystallized from acetone formed colourless needles, m.p. 142 °C (Found: C, 80.1; H, 5.8; CH₃O, 17.1%. Calc. for C₂₃H₂₀O₃: C, 80.2; H, 5.85; CH₃O, 18.0%). Light absorption: ϵ_{\max} 18,760 at 3250 Å.

(b) *7,4'-Dimethoxy-4-(p-methoxyphenyl)isoflav-3-en.*—The same quantities of reagents were used as in the last experiment but *p*-bromoanisole was substituted for bromobenzene. The product was an orange oil (1.8 g) from which an unidentified orange solid (0.11 g) separated from acetone. The mother liquors after stirring with ether and recrystallization of the solid obtained from ethanol gave colourless needles (73 mg), m.p. 141 °C (Found: C, 77.2; H, 5.95%. Calc. for C₂₄H₂₂O₄: C, 77.0; H, 5.9%). Light absorption: ϵ_{\max} 20,450 at 2475 Å; 18,500 at 3250 Å.

(c) *5,7,4'-Trimethoxy-4-phenylisoflav-3-en.*—When 5,7,4'-trimethoxyisoflavanone (1 g) was made to react with phenylmagnesium bromide according to the foregoing procedure the product (0.97 g) could be isolated without heating under reduced pressure. It formed colourless needles, m.p. 157 °C from ethanol (Found: C, 77.3; H, 6.0%. Calc. for C₂₄H₂₂O₄: C, 77.0; H, 5.9%). Light absorption: ϵ_{\max} 19,150 at 3200 Å.

(d) *5,7,4'-Trimethoxy-4-(p-methoxyphenyl)isoflav-3-en.*—By the same procedure 5,7,4'-trimethoxyisoflavanone (1 g) and *p*-anisylmagnesium bromide gave a product crystallizing from ethanol as colourless needles (0.92 g), m.p. 136 °C (Found: C, 74.3; H, 6.0; CH₃O, 30.1%. Calc. for C₂₅H₂₄O₅: C, 74.2; H, 6.0; CH₃O, 30.7%). Light absorption: ϵ_{\max} 18,910 at 3200 Å.

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References

- ANDERSON, E. L., and MARRIAN, G. F. (1939).—*J. Biol. Chem.* **127**: 649.
BRADBURY, R. B., and WHITE, D. E. (1953).—*J. Chem. Soc.* **1953**: 871.
MASSON, G. (1944).—*Rev. Canad. Biol.* **3**: 491.
ROBINSON, T. J. (1949).—*Aust. J. Exp. Biol. Med. Sci.* **27**: 297.
SCHONBERG, A., ROBSON, J. M., TADROS, W., and FAHIM, H. A. (1940).—*J. Chem. Soc.* **1940**: 1327.