(12) J. Schmutz, R. Hirt, and H. Lauener, *Helv. Chim. Acta*, **35**, 1168 (1952).
(13) V. A. Zagorevskii, D. A. Zykov, and E. K. Orlova, *J. Gen. Chem. USSR*, **30**, 3850 (1960).
(14) V. A. Zagorevskii, D. A. Zykov, and E. K. Orlova, *ibid.*, **31**, 523 (1961).
(15) V. A. Zagorevskii, D. A. Zykov, and L. P. Pronina, *ibid.*, **29**, 1004 (1959).
(16) C. Fitzmaurice and A. H. Wragg, British Patent 1,032,362 (1966).
(17) C. R. Jacobson, K. R. Brower, and E. D. Amstutz, *J. Org. Chem.*, **18**, 1117 (1953).
(18) W. Baker, G. G. Clarke, and J. B. Harborne, *J. Chem. Soc.*, 998 (1954).
(19) Z. Rappoport, Ed., "Chemistry of the Cyano Group," Wiley, New York, N. Y., 1971.
(20) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Amer. Chem. Soc.*, **77**, 1701 (1955).
(21) W. G. Finnegan, R. A. Henry, and R. Lofquist, *ibid.*, **80**, 3908 (1958).
(22) J. Dauphin, D. Chatonier, J. Couquelet, M. Payard, and M. Picard, *Labo-Pharma-Probl. Tech.*, **18**, 58 (1970).
(23) B. M. Ogilvie, *Immunology*, **12**, 113 (1967).
(24) R. I. Taber, D. D. Greenhouse, and S. Irwin, *Nature (London)*, **204**, 189 (1964).
(25) G. Woolfe and A. D. Macdonald, *J. Pharmacol. Exp. Ther.*, **80**, 300 (1944).
(26) Z. Jerzmanowska and K. Kostka, *Rocz. Chem.*, **37**, 413 (1963).
(27) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962, Chapter 2.

Photochemistry of Zearalenone and Its Derivatives

C. Allan Peters

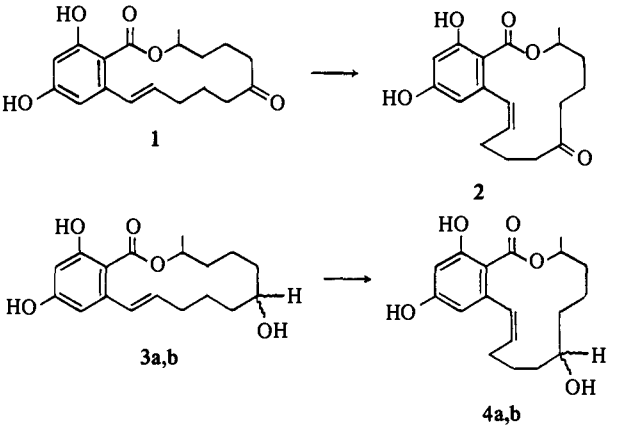
Research Department, Commercial Solvents Corporation, Terre Haute, Indiana 47808. *Received January 14, 1972*

In the course of studying the biological activity profile of zearalenone and several of its derivatives,[1,2] it seemed appropriate to examine the effect that molecular shape has on uterotropic activity.

From molecular models, it appeared that one of the most dramatic changes that could be made in the molecular shape was to convert the trans-1′,2′ double bond† in zearalenone to the cis arrangement. This cis-trans stereoisomerization can most easily be accomplished by a photochemical process.‡

Zearalenone (**1**) and each of the diastereomeric zearalenols (**3a, b**) were dissolved in methanol and irradiated until a photostationary state was reached. In each case, the photostationary state consisted of >97% of the cis isomer.

A comparison of the nmr spectra of **1** and **2** showed that the change in the chemical shift of the proton on C-1′, from δ 7.14 in **1** to 6.72 in **2**, along with the change in the coupling constant, $J_{1',2'}$, from 16 Hz in **1** to 11.5 Hz in **2**, clearly supported the cis assignment of stereochemistry about the carbon-carbon double bond in **2**. In addition, a number of other protons in the molecule had undergone shielding effects due to the change in molecular shape. For



example, the signal for the proton on C-5 of the aromatic ring is shifted upfield by 18 Hz due to a shielding effect by the carbon-carbon double bond. Other upfield shifts by the allylic protons on C-3′ (42 Hz) and the protons on C-5′ and C-7′ (22 Hz) are probably due to the shielding effect by the aromatic π-electrons as a result of the 14-membered ring being folded over the shielding cone of the aromatic ring. Similar shielding effects were observed for each of the diastereomeric zearalenols (**4a, b**).

Table I. Uterotropic Activity in Mice

Test compound[a]	Daily dose, μg/g of feed	Uterine wt, mg	% body wt
Control	25	11.5	0.049
1	25	28.2	0.114
2	25	25.7	0.107
3a	50	11.2	0.050
4a	50	32.1	0.139
	100	51.8	0.226
3b	6.25	19.1	0.079
4b	3.125	32.2	0.133
	6.25	49.3	0.208

[a] In each cis-trans pair, the trans isomer tested came from the same lot as the material used in the photochemical conversion to its corresponding cis isomer.

The uterotropic activity data are summarized in Table I. In zearalenone, the cis isomer has slightly less activity than the trans isomer, but in the zearalenols, both cis isomers have substantially more activity than their respective trans isomers.

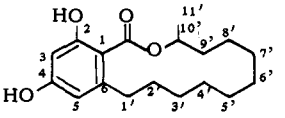
Experimental Section§

The following experimental procedure is representative for all the compounds used in this study.

cis-**Zearalenone (2).** A solution of *trans*-zearalenone (10.0 g) in 500 ml of methanol was placed in a 500-ml photochemical reactor equipped with a borosilicate glass immersion well. The system was purged overnight with nitrogen and then irradiated with a 450-W medium-pressure mercury lamp for 72–96 hr. The light yellow solution was treated with 1.0 g of KB charcoal and filtered; the methanol was removed under vacuum on a rotary evaporator to give 9.9 g of cream-colored solid. Recrystallization twice from methanol–water gave 8.8 g (88%) of *cis*-zearalenone (**2**) as white crystals, mp 134–135°. *Anal.* ($C_{18}H_{22}O_5$) C, H.

cis-**Zearalenols (4a and 4b).** The crude product obtained from

†The numbering system used throughout this paper for the zearalane system is as follows



‡For a summary of photochemical stereoisomerization of compounds containing isolated C=C, see ref 3.

§Melting points are uncorrected. Elemental analyses were performed in our laboratories. Spectra were recorded on the following instruments: uv, Bausch & Lomb Spectronic 505; ir, Perkin-Elmer Model 21 spectrophotometer; nmr, Varian Associates A-60A spectrometer (Me_2CO-d_6 as the solvent and TMS as the internal standard). All ir, uv, and nmr spectra are consistent with the assigned structures. Analyses are indicated only by symbols of the elements and the analytical results obtained for those elements were within ±0.4% of the theoretical values.

irradiation of 5-10 g of *trans*-zearalanol (**3a** or **3b**)# was purified by column chromatography on 200 g of SilicAR, CC-7, with 3% methanol-chloroform to give *cis*-zearalenol (**4a** or **4b**) as a white amorphous solid,** mp (**4a**) 124-128°, mp (**4b**) 126-131°. *Anal.* ($C_{18}H_{24}O_5$) C, H.

Uterotropic Assays. Stock solutions prepared in methanol were diluted and poured on small animal ration (Allied Mills), which was allowed to dry overnight at room temperature. Each test diet was further mixed in a high-speed blender for 1 min before being offered to eight adult castrate female mice for 5 days at 3 g per mouse per day. On day six the animals were sacrificed, and uteri were removed and weighed.

Acknowledgment. The author is grateful to Mr. Harold Burns for technical assistance, Mr. Carl Power for performing the uterotropic assays, and Mr. Bill Boyll for carrying out the analyses.

References

(1) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillete, *Nature (London)*, **196**, 1318 (1962).
(2) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).
(3) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, pp 56-58.

#Samples of the two diastereomeric *trans*-zearalenols were furnished by Dr. E. B. Hodge (Commercial Solvents Corp.).

**The *cis*-zearalenols could not be crystallized before or after chromatography from any of the many solvent systems tested and were contaminated with <3% of the corresponding trans isomer.

β-Adrenergic Blocking Agents of the Chromone and Xanthone Groups. II. Propranolol Type Derivatives†

P. Da Re,* G. P. Primofiore, and A. Bertelli

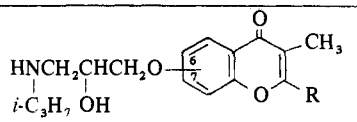
Institutes of General Chemistry and Pharmacology, University of Pisa, 56100 Pisa, Italy. *Received February 3, 1972*

In a preceding note on this subject,[1] some new heterocyclic β-adrenergic blocking drugs of the dichloroisoproterenol (DCI) type were reported. One of these, the 6-(1-hydroxy-2-isopropylaminoethyl)-2,3-dimethylchromone (I) was the most interesting, it showed a selective β-adrenergic blocking activity of the propranolol type[2] (with a potency ratio, in comparison with propranolol, of 0.1 but with LD_{50} 2.5 times lower) with membrane activity and was devoid of intrinsic sympathomimetic activity. It seemed logical to complete the preceding research with the preparation of the corresponding propranolol type derivatives, *i.e.*, compounds in which the isopropylaminoethanolic chain is separated from the supporting moiety by a methyleneoxy bridge. On the basis of the previous results[1] only the *N*-isopropyl derivatives have been taken into consideration. The basic chain, beside being in the position of the reference products, has been introduced also in position 7, for the chromone and flavone derivatives, and in position 3 for the xanthone analogs. The preparation of these products was easily brought about by condensing the selected hydroxy compounds with epichlorohydrin, followed by amination of the resulting epoxy derivatives with isopropylamine.

In Table I all the chromone and flavone derivatives prepared are shown, while the xanthone analogs are described in detail in the Experimental Section for illustrative purposes.

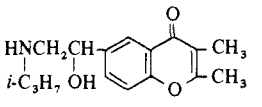
†This work was supported by a Grant from Consiglio Nazionale delle Ricerche, Rome.

Table I. Chromone and Flavone Derivatives

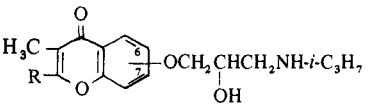


Compd[b]	R	Position of the basic chain	Mp, °C	Formula	Analyses
3	CH_3	6	174-176[a]	$C_{17}H_{24}ClNO_4$	C, H, Cl, N
6	CH_3	7	186-188[a]	$C_{17}H_{24}ClNO_4$	C, H, Cl, N
9	C_6H_5	6	115-117[a]	$C_{22}H_{26}ClNO_4$	C, H, Cl, N
12	C_6H_5	7	128-130[a]	$C_{22}H_{26}ClNO_4$	C, H, Cl, N

[a]Crystn solvent, MeOH-Et_2O. [b]The bases corresponding to compounds **3**, **6**, **9**, and **12** melted, respectively (ligroin), at 81-83°, 124-125°, 132-135°, 147-148°.



I



R = CH_3; C_6H_5

The new compounds have been evaluated for their β-adrenergic blocking activity in the following tests: (1) isolated atrial strips according to Kottegoda,[3] (2) isolated guinea pig colon according to Garry and Gillespie,[4] (3) blood pressure in anesthetized (urethan 1 g/kg ip) guinea pig.[5] Isoprenaline was used as β-stimulating agent. The inotropic effect (test 1), smooth muscle relaxing activity (test 2), and blood pressure fall (test 3) were not modified by the tested compounds up to 1×10^{-4} g/ml in the *in vitro* assays, and up to 10 mg/kg in the *in vivo* test. With the same experimental conditions propranolol at 1×10^{-5} g/ml and 1 mg/kg entirely inhibited the effects of isoprenaline. Surprisingly all the compounds prepared were devoid of β-blocking activity. This result seems to be in contrast with the observation that the β-adrenergic blocking activity of a DCI-type derivative is not notably affected by the introduction of a methyleneoxy bridge between the supporting moiety and the isopropylaminoethanolic side chain.[6]

Experimental Section‡

Preparation of the Epoxy Derivatives (General Procedure). A solution of 0.05 mole of the hydroxy derivative and 0.05 mole of NaOH in 50 ml of 50% aqueous EtOH was slowly added under stirring to 20 ml of epichlorohydrin and left to stand at room temperature for 12 hr. The sepd product was collected, washed (H_2O), and dried. The crude product was purified by column chromatography on alumina and elution with PhH, giving the desired product.

6-Epoxypropoxy-2,3-dimethylchromone (1) was obtained as a white crystalline product, mp 143-145° (from ligroin) (54% yield). *Anal.* ($C_{14}H_{14}O_4$) C, H.

7-Epoxypropoxy-2,3-dimethylchromone (4) was obtained as a white crystalline product, mp 104-106° (ligroin) (55% yield). *Anal.* ($C_{14}H_{14}O_4$) C, H.

6-Epoxypropoxy-3-methylflavone (7) was obtained as a white crystalline product, mp 115-118° (ligroin) (54.5% yield). *Anal.* ($C_{19}H_{16}O_4$) C, H.

7-Epoxypropoxy-3-methylflavone (10) was obtained as a white crystalline product, mp 129-131° (ligroin) (65% yield). *Anal.* ($C_{19}H_{16}O_4$) C, H.

2-Epoxypropoxyxanthone (13) was obtained as a white crystal-

‡All melting points were dtd in open glass capillaries, using a Büchi apparatus, and are uncorrected. All the compounds reported gave elemental analyses for C, H, Cl and N, within ±0.4% of the calculated values.