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.

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#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†

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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.

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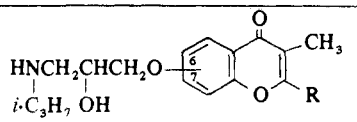
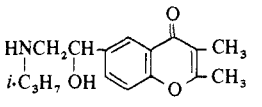
Table I. Chromone and Flavone Derivatives



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°.



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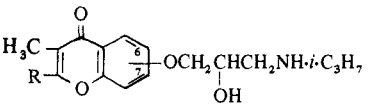

R = CH_3; C_6H_5

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.

line solid, mp 136–138° (ligroin) (65.6% yield). *Anal.* ($C_{16}H_{12}O_4$) C, H.

3-Epoxypropoxyxanthone (16) was obtained as a white crystalline product, mp 162–163° (ligroin) (71% yield). *Anal.* ($C_{16}H_{12}O_4$) C, H.

2-(3-Isopropylamino-2-hydroxypropoxy)xanthone (14). In a stainless vessel containing 5 g of 2-epoxypropoxyxanthone (13) (0.0186 mole) and 50 ml of BzH, a slight excess of isopropylamine (1.2 g, 0.02 mole) was added, and the mixture was kept, under stirring, at 50° for 12 hr. After removing of the solvent, the residue was crystallized from ligroin, giving 4 g (54% yield) of white product, mp 113–115°. *Anal.* ($C_{19}H_{21}NO_4$) C, H, N.

The hydrochloride salt (15) was obtained as a white solid, mp 222–224° (from MeOH–Et_2O). *Anal.* ($C_{19}H_{22}ClNO_4$) C, H, Cl, N.

3-(3-Isopropylamino-2-hydroxypropoxy)xanthone (17). In a similar manner, starting from 5 g (0.0186 mole) of compd 16, 3.2 g (54% yield) of white solid, mp 143–144° (ligroin), was obtained. *Anal.* ($C_{19}H_{21}NO_4$) C, H, N.

The hydrochloride salt (18) was obtained as a white solid, mp 220–222° (MeOH–Et_2O). *Anal.* ($C_{19}H_{22}ClNO_4$) C, H, Cl, N.

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Preparation of *N*-(2-Chloroethyl)-*N*-(2-hydroxyethyl)arylamines. Possible Intermediates to Potential Carcinolytic Agents Bearing Dissimilar Reactive Functions

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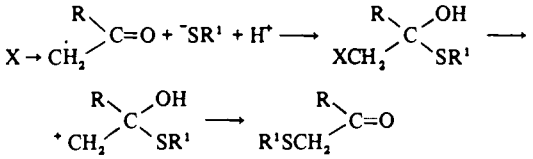
Although *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)arylamines are potentially useful intermediates in the preparation of bifunctional alkylating agents containing dissimilar reactive groupings, few syntheses of these compounds have been reported. Ross and his coworkers[1] prepared *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)anthranilic acid *via* the internal ester formed from the corresponding *N,N*-bis(2-hydroxyethyl) derivative. Yaguzhinskii and Chinaeva[2] applied a potentially more general procedure, the reaction of ethylene oxide with an *N*-(2-chloroethyl)arylamine, to the synthesis of *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)aniline (I).

Since *N,N*-bis(2-chloroethyl)arylamines bearing a wide range of carrying structures are known,[3] partial hydrolysis to the corresponding *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)-arylamines was investigated. Davis and Ross[4] have shown that, near neutrality, the rate constant ($k_1 = 13.8 \times 10^{-4}$ sec^{-1}) for the formation from 3-[4-bis(2-chloroethyl)aminophenoxy]propionic acid of the *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl) derivative was less than the value ($k_2 = 20.8 \times 10^{-4}$ sec^{-1}) for the hydrolysis of the latter. A similar relationship between k_1 and k_2 was obtained for a range of derivatives studied by Yaguzkinskii and Chinaeva.[2] Hence, the partial hydrolysis products do not accumulate under neutral conditions.

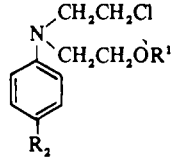
In contrast, when the hydrolysis of the three *N,N*-bis(2-chloroethyl)arylamines, aniline mustard [*N,N*-bis(2-chloroethyl)aniline],[5] *p*-hydroxyaniline mustard [*N,N*-bis(2-chloroethyl)-4-hydroxyaniline],[6] and chlorambucil {4-[4-bis(2-chloroethyl)aminophenyl]butyric acid},[1] was conducted in unbuffered aqueous acetonitrile, accumulation of the corresponding partial hydrolysis products (I–III) occurred, with little further hydrolysis to the *N,N*-bis(2-hydroxyethyl) derivatives. Clearly, the protonation of the basic nitrogen atom in the products of partial hydrolysis prevented further hydrolysis by the SN1 mechanism. Eventually, protonation of the more weakly basic *N,N*-bis(2-chloroethyl)arylamines proceeds as the hydrogen ion concentration rises, causing virtual cessation of the hydrolysis. In aqueous dioxan, partial hydrolysis is less complete when this terminal stage is approached, presumably owing to the lower dielectric constant of the medium. Since the above procedure exploits a feature inherent in the bis(2-chloroethyl)amino function, namely the lower pK_b of its derivatives compared with corresponding *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)-substituted analogs, it is potentially of general applicability.

The use of such an intermediate for the preparation of agents of mixed functionality is exemplified by the conversion of *N*-(2-chloroethyl)-*N*-(2-hydroxyethyl)aniline (I) into the halogenoacetyl derivatives (IV–VI). It has been suggested that the cross-linking of DNA to protein could be a significant factor contributing to the cytotoxic properties of bifunctional alkylating agents.[7] The halogenoacetyl group should confer reactivity toward thiol functions under physiological conditions according to the following mechanism.[8]

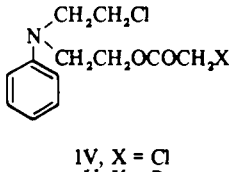


Hence the derivatives (IV–VI) might form cross-links between DNA and the cysteine residues of a protein molecule.

However, screening data revealed that the two compounds examined, IV and VI, had no curative effect on rats bearing the transplanted Walker 256 carcinoma at single intraperitoneal doses of up to 125 mg/kg for the chloro derivative (IV) (LD_{50} 595 mg/kg) and 25 mg for the iodo derivative (VI) (LD_{50} 25 mg/kg). The higher toxicity of the iodo derivative (VI) is consistent with the greater reactivity toward cellular thiol functions which would be conferred by the superior inductive effect (see above mechanism) of the iodo grouping. In contrast, the corresponding bis-nitrogen mustard, *N,N*-bis(2-chloroethyl)aniline gave 90% inhibition of tumor growth at a dose (ED_{90}) of 13.6 mg/kg.



I, $R^1 = R^2 = H$
II, $R^1 = H$; $R^2 = OH$
III, $R^1 = H$; $R^2 = CH_2CH_2CH_2CO_2H$



IV, X = Cl
V, X = Br
VI, X = I

The LD_{50} was 146 mg/kg, giving a therapeutic index (LD_{50}/ED_{90}) of 10.8.[9] Presumably, therefore, the reaction of the halogenoacetyl moiety is preponderantly with thiol groups not in proximity to DNA. Ross pointed out that compounds, such as halogeno ketones, unsaturated lactones, and vinyl sulfones, which react with thiol groups