ether mixtures, followed by crystallization from acetone–hexane gave 3.17 g of the tetrahydropyranyl ether, mp 148.5° dec. The analytical sample had mp 152.5° dec, $[\alpha]^{23}D$ +65°.

Anal. Calcd for $C_{29}H_{42}FO_6$: C, 68.74; H, 8.55; F, 3.75. Found: C, 68.53; H, 8.43; F, 3.94.

6α,9α-Difluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-*t*-butylacetate (V, R = $(CH_3)_3CCH_2CO$) was prepared from the corresponding 3β-alcohol V (R = H) and *t*-butylacetyl chloride in pyridine; mp 246–248° dec, $[\alpha]^{23}D$ +74.4°.

Anal. Calcd for $C_{30}H_{44}F_2O_6$: C, 66.89; H, 8.23; F, 7.05. Found: C, 66.64; H, 8.19; F, 7.03.

6α-Fluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-*t*-butylacetate (VI, R = $(CH_3)_3CCH_2CO$) was prepared from the corresponding 3β-alcohol VI (R = H); mp 209–210° dec, $[\alpha]^{23}D$ +58°.

Anal. Calcd for $C_{30}H_{45}FO_6$: C, 69.20; H, 8.71; F, 3.65. Found: C, 69.08; H, 8.62; F, 3.76.

6α-Fluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-benzoate (VI, R = C_6H_5CO) was prepared from the corresponding 3β-alcohol VI (R = H) and benzoyl chloride in pyridine; mp 168–170° dec, $[\alpha]^{23}D$ +49°.

Anal. Calcd for $C_{31}H_{39}FO_6$: C, 70.70; H, 7.46; F, 3.61. Found: C, 70.42; H, 7.21; F, 3.77.

Derivatives of 3,4-Diphenylchromanes as Estrogens and Implantation Inhibitors

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A number of substituted 3,4-diphenylchromanes have been prepared from isoflavanones. Their chemical, spectral, and biological properties, *i.e.*, estrogenic and antifertility activity, are discussed.

Several years ago Gaunt and co-workers[1] emphasized the necessity of the extension of classical endocrinology into broad endocrine pharmacology. While classical endocrinology is primarily concerned with the isolation, synthesis, and improvement of natural hormones, endocrine pharmacology would imply the study of nonhormonal compounds to elucidate hormonal and enzymic mechanisms and by this route to detect substances which would be able to restore deranged endocrine homeostasis.

Diverse nonsteroidal compounds such as amphenones, pyridyl ketones, aminoindenes,[2] 2,3-diphenylindenes,[3] 1,2-diaryldihydro- and 1,2-diaryltetrahydronaphthalenes,[4] isoflavones,[5] 2,2-dialkyl-3-isoflavens,[6] diarylpropionitriles,[7] 3,4-diphenylcoumarins,[8] and 2,3-diphenylbenzofurans[9] have shown specific interactions with endocrines. Moreover, a recent communication from our laboratories outlines the synthesis and biological properties of some new *cis* and *trans* isomers of 1,2,3,4-tetrahydro-1,2-diarylnaphthalene derivatives.[4c] It was shown that some of these compounds exhibited marked estrogenic activity as well as potent antifertility activity in the female rat. It has been noted also that 3-pyridyl-4-chromone derivatives have specific effects on the adrenal glands and in the gonads.[10] Hence it was our aim to investigate compounds structurally related to both the 1,2-diarylnaphthalenes and chromones which would possess little or no estrogenic potency while still retaining or possibly eliciting an increased antifertility activity. Therefore, the 3,4-diphenylchromanes, a group of compounds which had not been explored heretofore, were selected for study in this regard.

Over a decade ago Bradbury and White showed that isoflavones and their derivatives possessed estrogenic activity.[11] Some of these were isolated from subterranean clover which had been found to be responsible for infertility in sheep in Western Australia. Bradbury prepared 3,4-diaryl-substituted chromenes by treating a substituted phenyl Grignard reagent with the corresponding isoflavanones.[12] The isoflavanones were derived from the isoflavones by catalytic hydrogenation.[13] Inove recently described a method for the synthesis of 7-methoxyisoflavanone from 7-methoxy-3-hydroxyisoflavanone or 7-methoxy-3-acetoxyisoflavanone by zinc dust–acetic acid reduction.[14] However, since both of these methods do not lend themselves to a convenient preparation of 3-phenylchromanones, the method of DaRe and Verlicchi was used in the course of our study.[15] These investigators found that the condensation of formaldehyde with an *o*-hydroxyphenyl benzyl ketone derivative in basic medium yields the desired isoflavanone directly.

Thus, *o*-hydroxyphenyl *p*-chlorobenzyl ketone and paraformaldehyde were allowed to react in aqueous sodium hydroxide solution at 55° to afford 3-*p*-chlorophenyl-4-chromanone (I) in 64% yield (see Scheme I). This substance was then treated with the *p*-methoxy-

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(2) (a) W. L. Bencze and M. J. Allen, *J. Med. Pharm. Chem.*, **1**, 395 (1959); (b) J. J. Chart and H. Sheppard, *ibid.*, **1**, 407 (1959); (c) W. L. Bencze and L. I. Barsky, *ibid.*, **5**, 1298 (1962); (d) J. J. Chart, H. Sheppard, R. Mowles, and N. Howie, *Endocrinology*, **71**, 479 (1962).

(3) (a) D. Lednicer, J. C. Babcock, S. C. Lyster, J. C. Stucki, and G. W. Duncan, *Chem. Ind.* (London), 2098 (1961); (b) D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 52 (1965), and references therein.

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(10) W. L. Bencze, U. S. Patent 3,178,442 1965; *Chem. Abstr.*, **61**, 1840 (1964).

(11) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 3447 (1951); 871 (1953).

(12) R. B. Bradbury, *Australian J. Chem.*, **6**, 447 (1953).

(13) E. L. Anderson and G. F. Marrian, *J. Biol. Chem.*, **127**, 649 (1939).

(14) N. Inove, *Sci. Rept. Tohoku Univ., First Ser.*, **45**, 68 (1961).

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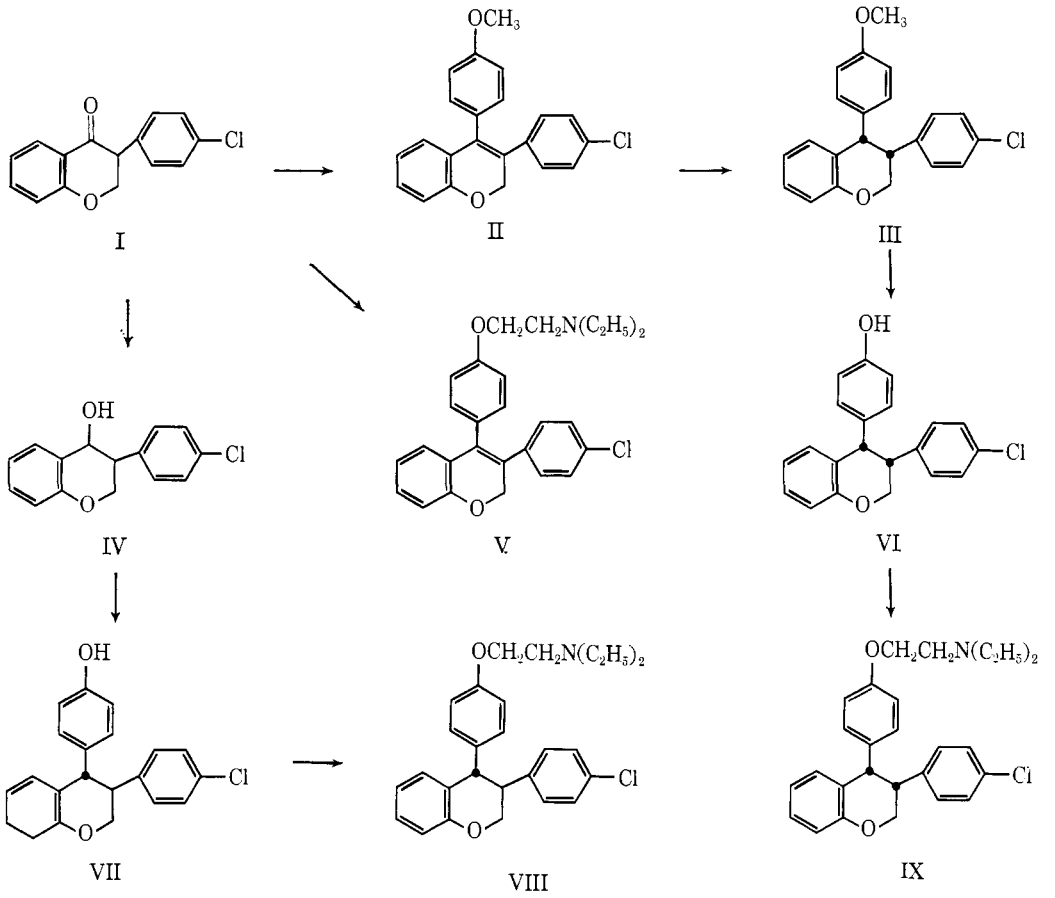
Scheme I

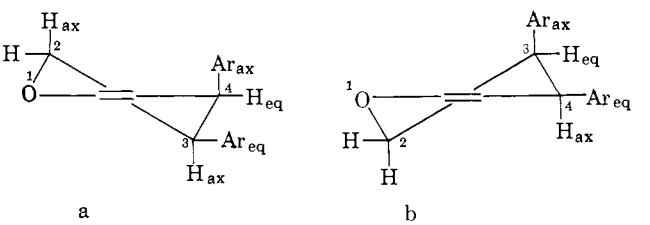


phenylmagnesium bromide, and the resulting tertiary alcohol was dehydrated to give II. Under similar conditions, the condensation of *p*-(2-diethylaminoethoxy)phenylmagnesium bromide with I yielded V. Catalytic hydrogenation of II in ethyl acetate at atmospheric pressure formed in 70% yield *cis*-3-*p*-chlorophenyl-4-*p*-methoxyphenylchromane (III). The stereochemical assignment was made on the basis of its mode of formation, *i.e.*, *cis* addition of hydrogen by catalytic reduction of an olefin. Moreover, nmr studies supported this assignment (*vide infra*). Compound III then was converted to the phenol VI by heating with pyridine hydrochloride. Alkylation of VI with 2-diethylaminoethyl chloride resulted in a 46% yield of *cis*-3-*p*-chlorophenyl-4-[*p*-(2-diethylaminoethoxy)phenyl]chromane (IX).

The synthesis of the corresponding *trans* isomer was achieved by an alternate route. Sodium borohydride reduction of I gave a *cis–trans* mixture of secondary alcohol IV which in our hands resisted separation. Therefore, the mixture was carried through the next reaction step. Friedel–Crafts alkylation of phenol with 3-*p*-chlorophenyl-4-chromanol resulted in the formation of a mixture of phenolic products from which the *trans* isomer VII was isolated. This compound was distinctly different in physical and spectral properties from the *cis* phenol (VI). The *trans* basic ether VIII was accordingly prepared by the previously described method.

The other members of this series, *i.e.*, the chromenes of Table I and the *cis* and *trans* chromane isomers outlined in Tables II and III, respectively, were synthesized according to the sequences described above.

Though it is difficult to determine the preferred conformation of flavans[16] as well as isoflavans, a number of interesting conclusions can be drawn from the pmr spectra. In both the *cis* and *trans* derivatives the C-3 hydrogen is a broad multiplet at approximately 3.6 and 3.3 ppm, respectively. For the *cis* compounds the width of the proton multiplet is approximately 15–20 cps and for the *trans* isomers it is 25–30 cps. If one assumes that the preferred *cis* conformations a and b are as shown, *i.e.*, to obtain a proton spread

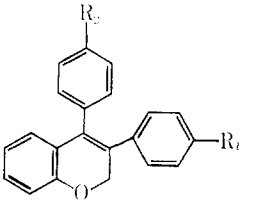


of 15–20 cps for the C-3 proton in the *cis* compounds, this proton must be axial interacting with the axial C-2 proton. The greater width of this area for the *trans* compounds must involve another pseudo-axial interaction from C-4. Thus, the substituents of the *trans* compounds must be pseudo-diequatorial and for the *cis* compounds the C-3 substituent is equatorial and C-4 is pseudo-axial. This relationship would also provide an explanation for the more shielded position of the C-3 hydrogen in the *trans* compounds since in these examples the C-3 proton and the aromatic ring

(16) J. W. Clark-Lewis, L. M. Jackman, and T. H. Spotswood, *Australian J. Chem.*, **17**, 632 (1964).

TABLE I

3,4-DIPHENYL-3-CHROMENES

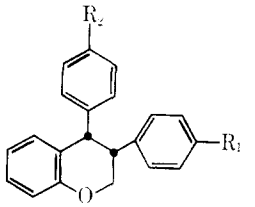


No.	R_1	R_2	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
1	H	H	133–135[a]	85	$C_{21}H_{16}O$	88.70	88.63	5.67	5.74
2	H	OCH_3	123–125[a]	27	$C_{22}H_{18}O_2$	84.05	83.97	5.77	5.51
3 (II)	Cl	OCH_3	156–158[a]	29	$C_{22}H_{17}ClO_2$	75.75	75.80	4.91	4.92
4 (V)	Cl	$OCH_2CH_2N(C_2H_5)_2$	202–204[b]	10	$C_{27}H_{28}ClNO_2$	74.72	74.76	6.50	6.76
5	Cl	OCH_3	156–157[a]	9	$C_{22}H_{15}D_2ClO_2$	75.31	75.93	5.46	6.06

[a] Recrystallized from ethanol. [b] Recrystallized from 2-propanol.

TABLE II

cis-3,4-DIPHENYLCHROMANE

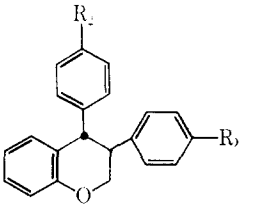


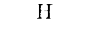
No.	R_1	R_2	Bp (mm) or mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
6	H	H	89–92[a]	98	$C_{21}H_{18}O$	88.08	87.83	6.34	6.30
7	H	OH	152–153[b]	97	$C_{21}H_{18}O_2$	83.42	83.39	6.00	6.23
8	H	OCH_3	98–99[c]	72	$C_{22}H_{20}O_2$	83.51	83.19	6.37	6.36
9	H	$OCH_2CH_2N(C_2H_5)_2$	200 (1)	30	$C_{27}H_{31}NO_2$	80.76	81.03	7.78	7.85
10 (VI)	Cl	OH	147–152[b,d]	74	$C_{21}H_{17}ClO_2$	74.88	74.42	5.09	5.10
11 (III)	Cl	OCH_3	115–117[e]	70	$C_{22}H_{19}ClO_2$	75.32	75.55	5.46	5.91
12 (IX)	Cl	$OCH_2CH_2N(C_2H_5)_2$	140–145 (1)	46	$C_{27}H_{30}ClNO_2$	74.37	75.45	6.94	6.66
13	Cl	OCH_3	109–110[e]	90	$C_{22}H_{17}D_2ClO_2$	74.89	74.47	6.00	6.48

[a] Recrystallized from ethanol. [b] Recrystallized from benzene–pentane. [c] Recrystallized from benzene–hexane. [d] Sublimed. [e] Recrystallized from 2-propanol.

TABLE III

trans-3,4-DIPHENYLCHROMANE



No.	R_1	R_2	Bp, °C (mm)	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
14	H	OH	Amorphous	81	$C_{21}H_{18}O_2$	83.42	83.61	6.00	6.03
15	H	$OCH_2CH_2N(C_2H_5)_2$	123–130 (1)	53	$C_{27}H_{31}NO_2$	80.76	80.98	7.78	7.98
16	H		140–150 (0.6)	60	$C_{27}H_{29}NO_2$	81.17	81.53	7.32	7.82
17 (VII)	Cl	OH	Amorphous	90	$C_{21}H_{17}ClO_2$	74.88	74.76	5.09	5.26
18 (VIII)	Cl	$OCH_2CH_2N(C_2H_5)_2$	175 (0.55)	59	$C_{27}H_{30}ClNO_2$	74.37	74.40	6.94	6.62

are on the same side and the shielding effects of the latter would be felt.

Both the C-4 and C-2 protons overlap at approximately 4.3 ppm and as a result it is difficult to obtain definitive coupling constants of the C-4 proton. However, in each isomer the AB complex of the C-2 protons have characteristic shapes thus facilitating the distinction between them.

To obtain the C-4–C-3 coupling constant for the *cis* compounds, the 2,2-dideuterio-labeled chromane related to III was synthesized. The coupling constant ($J_{3,4}$) for this substance was found to be 4.5 cps. As

already shown by Clark-Lewis, *et al.*,[16] in the flavan series, this J value does not clearly define the precise conformation of our *cis* compounds.

Biological Data.—The structure–activity relationship of the compounds shown in Tables I–III was studied.

Estrogenic Activity.—To determine estrogenic activity, the compounds were placed in suspension with carboxymethylcellulose and administered to immature female rats weighing 40–50 g at a dose of 2.5 mg/kg for 3 days by subcutaneous injection. On the fourth day the uterus was removed, cleaned of adhering tissue, and weighed. The estrogenic activity where present, was compared to the response on the uterus elicited by 2.0 μg/kg of 17β-estradiol. Compound **1** (Table I) showed marked estrogenic activity down to a dose of 80 μg/kg. The other members of this series (**2–4**) had only weak activity. In the *cis*-3,4-diphenylchromanes series (Table II), **6** showed moderate estrogenic activity. In contrast to **1**, the activity was much less. Compounds **7–12** in this series had little or no effect on the uterus of the treated rats. The *trans*-3,4-diphenylchromanes (Table III) all produced moderate to marked estrogenic effects when given to immature female rats.

Antiestrogenic Activity.—Tests were performed with those compounds having estrogenic activity to determine if they could block the estrogenic effect of 17β-estradiol when given concomitantly to immature female rats for 3 days. No antiestrogenic response was observed.

Antifertility Activity.—Compounds **14–18** (Table III) were administered orally at a dose of 1.0 mg/kg to adult female rats (180–200 g) beginning on day 1 postmating and continued for 4 consecutive days. On the twelfth day the rats were sacrificed and the stage of pregnancy was determined. The purpose of the study was to see if these estrogenically active compounds were capable of blocking implantation of the fertilized ova in the uterus. With the exception of **18** which gave 100% protection against implantation at the dose tested, all the others were inactive as antifertility compounds.

Experimental Section[17]

3-*p*-Chlorophenylchromanone (I).—Paraformaldehyde (3.0 g, 0.1 mole) dissolved in 20 ml of 50% NaOH and 60 ml of water was added to *o*-hydroxyphenyl *p*-chlorobenzyl ketone (24.65 g, 0.1 mole) dissolved in warm aqueous base (30 ml of 50% NaOH and 1500 ml of water) and the solution was stirred at 55°. A solid began to form within a short time. After 1 hr 13.8 g of crude product was filtered off. A second mole of paraformaldehyde (3.0 g) was added to the filtrate and the solution was stirred 1 hr whereupon 8.1 g more of crude product was collected. Recrystallization of the combined products from ethanol yielded 16.6 g (64%) of pure I, mp 112–115°, infrared (Nujol) 1680 s cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.56; H, 4.38.

3-*p*-Chlorophenyl-2,2-dideuteriochromanone.—The above general procedure was used for the preparation of 3-*p*-chlorophenyl-2,2-dideuteriochromanone with the following exception. The formaldehyde-d_2 obtained from Merck Sharp and Dohme of Canada Ltd. as the Eu-polyoxymethylene form was difficulty soluble in aqueous NaOH. The formaldehyde-d_2 (4.38 g, 0.0177 mole) was stirred in 2 N NaOH (4.2 ml) and 27 ml of water for 2 hr at 60°. After filtering the undissolved material, a clear solution was obtained which was then added to *o*-hydroxyphenyl *p*-chlorobenzyl ketone (4.38 g, 0.0177 mole) dissolved in warm aqueous base (21 ml of 2 N NaOH and 10 ml of water). This solution was stirred at 55° for 2 hr. The white solid was filtered off and recrystallized from ethanol to yield 1.0 g (22%) of the 2,2-dideuterio derivative of I, mp 112–114°.

Anal. Calcd for $C_{15}H_9D_2ClO_2$: C, 69.10; H, 5.03. Found: C, 69.45, H, 5.16.

3-*p*-Chlorophenyl-4-methoxyphenyl-3-chromene (II).—To 3-*p*-chlorophenyl-4-chromanone (5.18 g, 0.02 mole) in 30 ml of tetrahydrofuran (THF) there was added *p*-methoxyphenylmagnesium bromide [prepared from 0.48 g (0.02 g-atom) of magnesium and 3.74 g (0.02 mole) of *p*-bromoanisole] in 120 ml of THF and the mixture was refluxed 14 hr. Saturated NH_4Cl was then added and the solvent was removed under reduced pressure. Water was added to the residue and the aqueous solution was extracted with ether. After the ether extract was dried ($MgSO_4$) and the solvent was removed, the light brown oil was heated at 190–200° for 3 hr. Crystallization from ethanol yielded 2 g (29%) of pure product: mp 156–158°; infrared (Nujol), 1628 cm^{-1}; ultraviolet, λ_{max} 243 mμ (ϵ 24,390), 284 sh (10,530), 304 (11,120), 325 (11,440).

***cis*-3-*p*-Chlorophenyl-4-*p*-methoxyphenylchromane (III).**—3-*p*-Chlorophenyl-4-*p*-methoxyphenyl-3-chromene (1.5 g, 0.0043 mole) in 150 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 500 mg of 10% Pd–C until the hydrogen uptake ceased. After removing the catalyst by filtration, the solvent was removed *in vacuo* resulting in a light oil which crystallized on addition of 2-propanol yielding 1.1 g (70%) of pure product: mp 115–117°; infrared (Nujol), no band above 1610 cm^{-1}; ultraviolet, λ_{max} 222 mμ (ϵ 9140), 275 (4550), 283 (3900).

3-*p*-Chlorophenyl-4-chromanol (IV).—Sodium borohydride (1.5 g, 0.04 mole) was added to 3-*p*-chlorophenylchromanone (8.0 g, 0.031 mole) dissolved in 150 ml of ethanol and the mixture was refluxed for 2 hr. After the solvent was removed under reduced pressure water was added to the residue and the resulting solution was extracted with ether. After drying the extract ($MgSO_4$) the solvent was removed *in vacuo* to yield white crystals: mp 105–120°; infrared (melt), 3300 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03; Cl, 13.61. Found: C, 69.14; H, 4.81; Cl, 13.59.

3-*p*-Chlorophenyl-4-[*p*-(2-diethylaminoethoxy)phenyl]-3-chromene. (V).—To 3-*p*-chlorophenyl-4-chromanone (5.0 g, 0.019 mole) in 30 ml of THF there was added *p*-(2-diethylaminoethoxy)phenylmagnesium bromide [prepared from 0.47 g (0.019 g-atom) of magnesium and 5.3 g (0.019 mole) of *p*-(2-diethylaminoethoxy)bromobenzene] in 100 ml of THF and the mixture refluxed 18 hr. Saturated NH_4Cl was added and the organic solvent was removed under reduced pressure. After the addition of water to the residue the aqueous portion was extracted with ether. Upon concentration of the ether extract 5% aqueous HCl and ethanol were added. The solution was refluxed for 30 min whereupon the ethanol was removed. Water was added to the aqueous solution and this was extracted with ether. The dried ether extract was then evaporated to dryness to yield 2.05 g of the starting ketone. The aqueous portion was then basified and extracted with ether. Solvent removal yielded a yellow oil which solidified on standing. Recrystallization from 2-propanol gave 0.45 g of pure V: mp 202–204°; infrared (Nujol), 1620 cm^{-1} (C=C); ultraviolet, λ_{max} 242 mμ (ϵ 25,000), 284 sh (10,830), 304 (11,580), 322 (11,610).

***cis*-*p*-Chlorophenyl-4-*p*-hydroxyphenylchromane (VI).**—*cis*-3-*p*-Chlorophenyl-4-*p*-methoxyphenylchromane (1.07 g, 0.0028 mole) was added to pyridine hydrochloride (prepared from 7 ml of pyridine and 12 ml of concentrated HCl by distilling until the temperature was 218°) and refluxed for 35 min. The hot solution was poured onto ice and the solid was filtered off. Recrystallization of this material from benzene–pentane gave 0.72 g (74%) of the desired product: mp 147–152°; infrared (Nujol), 3409, 3356 cm^{-1} (OH); ultraviolet, λ_{max} 201 mμ (ϵ 108,050), 224 sh (39,510), 276 (5260), 284 (4510).

***trans*-3-*p*-Chlorophenyl-4-*p*-hydroxyphenylchromane (VII).**—A solution of 3-*p*-chlorophenyl-4-chromanol (7.7 g, 0.0288 mole) and phenol (2.0 g, 0.0213 mole), dissolved in 200 ml of benzene and 50 ml of hexane, was added dropwise with cooling to $AlCl_3$ (5.0 g, 0.0375 mole) and phenol (4.0 g, 0.0426 mole). The reddish

(17) All melting points were determined with a Thomas–Hoover melting point apparatus. Pmr spectra were taken in dilute $CDCl_3$ solutions containing $(CH_3)_4Si$ as an internal standard on a Varian A-60 spectrometer. The infrared spectra were obtained on a Perkin-Elmer spectrophotometer, Model 21. The ultraviolet spectra were determined in methanol solutions and were taken on a Cary Model 14 spectrophotometer.

mixture was stirred at room temperature overnight and then poured into ice–HCl. The acidic solution was extracted with ether. After removal of solvent and excess phenol under reduced pressure a light tan glass was obtained: ultraviolet, λ_{max} 201 mμ (ε 79,370), 220 sh (28,040), 276 (4530), 284 sh (3900).

cis-**3-*p*-Chlorophenyl-4-[*p*-(2-diethylaminoethoxy)phenyl]-chromane (IX).—To a cooled solution of *cis*-3-*p*-chlorophenyl-4-*p*-hydroxyphenylchromane (0.50 g, 0.00149 mole) in 1 ml of dimethylformamide and 3 ml of toluene there was added 50% NaH in mineral oil (0.1 g, 0.02 mole). After stirring for a few minutes N-(β-chloroethyl)diethylamine (0.2 g, 0.00149 mole) was added, and the mixture was stirred overnight. After the solid was filtered off and washed with benzene, the filtrate was concentrated under reduced pressure. Water was added and the aqueous mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and filtered, and the solvent was removed to yield a clear oil which was distilled. In this way 300 mg (46%) of the *cis* basic ether, bp 140–149° (1 mm), was obtained; ultraviolet, λ_{max} 222 mμ (ε 28,680), 276 (4780), 284 (4060).

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Effect of Organic Compounds on Reproductive Processes. III. Alkylating Agents Derived from Various Diamines

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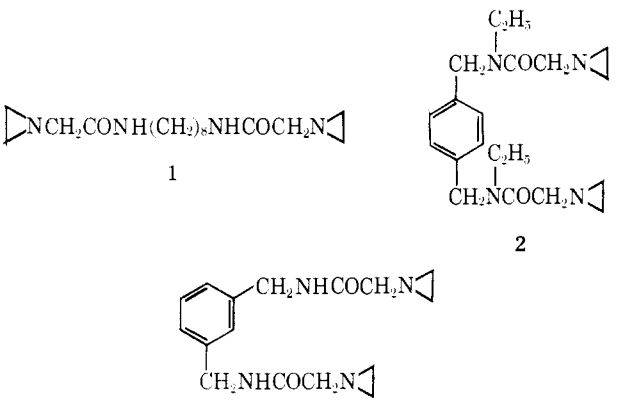
Alkylating agents derived from α,ω-alkylenediamines were synthesized and evaluated as chemosterilants in the housefly (*Musca domestica* L.). Chemosterilant activity varied with the distance between the two alkylating groups. Optimum activity was found in N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine and N,N′-bis(aziridineacetyl)-1,9-nonamethylenediamine.

As a continuation of our studies on the effect of organic compounds on reproductive processes, we have pursued the original lead[1] from compound **1**, N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine, to include the synthesis and evaluation in houseflies as chemosterilants of a group of N,N′-bis(aziridineacetyl)-diamines. In the case of the xylylenediamine derivatives previously prepared[1] it was found that the N,N′-diethyl derivative (**2**) was inactive as an inhibitor of reproduction in the housefly (*Musca domestica* L.) while **3** was active. This finding led us to suspect that the amide NH was essential for activity. We have now investigated this more thoroughly by the synthesis of N,N′-dimethyl-N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine (**21**) and N,N′-dimethyl-N,N′-bis(aziridineacetyl)-1,6-hexamethylenediamine (**20**). Both of these compounds were completely inactive toward inhibition of reproduction in houseflies when fed at the 1 wt % level in food. These results are in contrast to the activity of the corresponding compounds in which the amide NH was present (**1** and **13**).

In order to explore the relationship between the distance separating the two aziridinyl groups and activity as chemosterilants for houseflies the series of N,N′-bis(aziridineacetyl)-α,ω-diamines (**13**–**18**) was synthesized. These compounds were prepared from the corresponding N,N′-bis(bromoacetyl)-α,ω-diamines (**4**–**9**) by reaction with aziridine in the presence of anhydrous potassium carbonate as previously reported.[1] The properties of these alkylating agents are shown in Tables I and II along with the N,N′-dimethyl derivatives (**11**, **12**, **20**, and **21**) and the N-cyclohexyl derivatives (**10** and **19**).



1

2

3

$(CH_3)_2NCH_2CONH(CH_2)_8NHCOCH_2N(CH_3)_2$

22

$CH_3(CH_2)_7NHCOCH_2X$

23, X = Br
24, X = N

$CH_3O_2CNH(CH_2)_8NHCO_2CH_3$

25

$H_3CNH(CH_2)_8NHCH_3$

26

Two of the aziridineamides (**14** and **19**) were obtained as syrups which were converted to the crystalline chloroethylamine hydrochlorides by treatment with dry HCl in ether and characterized as such.

The activity as housefly chemosterilants of hexamethylphosphoramide and hexamethylmelamine,[2] comparable to that of the corresponding aziridine derivatives Tepa and Tretamine, led us to synthesize N,N′-

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(2) S. C. Chang, P. H. Terry, and A. B. Borkovec, *Science*, **144**, 57 (1964).