The nmr spectra, obtained at room temperature from about 20% solutions in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, were recorded on a Varian A-60 instrument. The *trans* isomer (**4**) showed an N-methyl at 141, a C-methyl at 83, and a split methyl at 77 cps with $J = 7$ cps. The *cis* isomer (**3**) had an N-methyl signal at 145, a C-methyl at 86, and a split methyl at 52 cps with $J = 7$ cps.

trans-**1,3,4-Trimethyl-2-(1-naphthylmethyl)-1,2,3,6-tetrahydropyridine Hydrochloride (6).**—The Grignard reagent from 97 g of 1-chloromethylnaphthalene and 13.3 g of Mg in 500 ml of ether was added to 1,3,4-trimethylpyridinium bromide under 500 ml of ether. After 1 hr, the mixture was filtered, and the filtrate was added to 300 g of ice and 105 ml of 60% $HClO_4$ with stirring. The inorganic salts were removed by filtration and the filter cake (53 g) was washed with ether to give, from the filtrate, 65.4 g of white crystals (**5**) melting at 103–119° dec. This perchlorate (55 g) was stirred with 60 ml of H_2O and 300 ml of ether, while a solution of 35 g of NaCN in 50 ml of H_2O was added to give 1,3,4-trimethyl-2-(1-naphthylmethyl)-6-cyanopyridine as a solution in ether. The ether layer was separated and concentrated to a small volume. Then, 80 ml of H_2O was added, followed by the slow addition of 80 ml of concentrated HCl. This caused vigorous evolution of HCN; the temperature rose to 70°. When the reaction had moderated, 320 ml of $CHCl_3$ was added, and the mixture was warmed 3 hr on the steam bath under reflux. The $CHCl_3$ and some of the H_2O were removed *in vacuo* to give *trans*-2,3-dihydro-1,3,4-trimethyl-2-(1-naphthylmethyl)pyridinium chloride as an orange oil suspended in H_2O. Fifty grams of NaCN were added, and the resulting *trans*-1,2,3,6-tetrahydro-1,3,4-trimethyl-2-(1-naphthylmethyl)-6-cyanopyridine was extracted with ether. Removal of the ether left 46 g of orange-brown syrup. This, in 250 ml of ethanol, was reduced with 12 g of $NaBH_4$ in 50 ml of H_2O. Work-up in the usual way gave 27.5 g of product which readily gave a crystalline hydrochloride **6**, mp 250–252° after one recrystallization from 2-propanol.

Anal. Calcd for $C_{19}H_{23}N \cdot HCl$: C, 75.61; H, 8.02; N, 4.64. Found: C, 75.54, 75.88; H, 7.91, 7.79; N, 4.55, 4.53.

The nmr spectrum of a 20% trifluoroacetic acid solution, using an external TMS standard, showed seven aromatic hydrogens at 435–470, one vinyl hydrogen at 325, a methyl singlet at 109, and a doublet at 74 cps.

Cyclization of 5 g of **6** with 5 g of $AlCl_3$ in 25 ml of CS_2 gave a 66% yield of crude material melting at 117–123°. Tlc showed that this was almost all **4** with a few per cent of **3** and a small amount of another material.

1,2,3,4,5,6-Hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—Compound **3** (42 g) was treated with 17 g of BrCN in $CHCl_3$ and the resulting N-cyano compound was hydrolyzed in the usual manner with 640 ml of 6% HCl to give 30.5 g of crude norbase. This was distilled to give 28.1 g (71%) of product boiling at 154° (0.6 mm). The hydrochloride, after recrystallization from ethanol, melted at 286–290°.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.11; H, 7.71; N, 4.87. Found: C, 74.86; H, 7.52; N, 5.04.

In like manner, 20 g of **4** gave 15.1 g (80%) of norbase boiling at 162–166° (0.9 mm). This gave a hydrochloride showing only one spot on tlc and decomposing at 330–337°.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: N, 4.87; Cl, 12.32. Found: N, 5.02; Cl, 12.54.

3-Cyclopropylcarbonyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—A solution of 7.6 g of *cis*-norbase in 50 ml of $CHCl_3$ and 4.6 ml of Et_3N was treated with 3.2 g of cyclopropanecarbonyl chloride in 25 ml of $CHCl_3$. The resulting solution was washed with H_2O, dilute HCl, and aqueous $NaHCO_3$. Concentration gave 9.8 g of light orange oil. Distillation of 7.7 g of this gave 0.3 g boiling at 60–192° (0.1 mm) and 6.0 g boiling at 192–197° (0.1 mm).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 82.63; H, 7.64; N, 4.53.

In like manner, the *trans* isomer was prepared. The product, after recrystallation from ethyl acetate–hexane, melted at 139.0–140.8° (cor).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 82.82; H, 7.97; N, 4.64.

3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—Reduction of 10.0 g of the *cis*-cyclopropylcarbonyl compound with 3 g of $LiAlH_4$ gave 9.6 g of clear, viscous oil which crystallized on standing. Three recrystallizations from aqueous ethanol gave 5.3 g melting at 78–81° (cor).

Anal. Calcd for $C_{22}H_{27}N$: C, 86.50; H, 8.91; N, 4.59. Found: C, 86.43; H, 8.74; N, 4.54.

In like manner the *trans* isomer was prepared. The base did not crystallize, but was converted to the hydrochloride. This was recrystallized from 2-propanol to give the pure product in 73% over-all yield from the amide. The hydrochloride melted at 249.5–251.5° (cor).

Anal. Calcd for $C_{22}H_{27}N \cdot HCl$: C, 77.28; H, 8.25; N, 4.10. Found: C, 77.09; H, 8.32; N, 4.07.

3-Cyclobutylmethyl-1,2,3,4,5,6-hexahydro-*cis*-6,13-dimethyl-2,6-methanonaphth[1,2-*d*]azocine.—To 8.5 g of *cis*-norbase in 50 ml of $CHCl_3$ and 5.1 ml of Et_3N was added 4.3 g of cyclobutylcarbonyl chloride in 25 ml of $CHCl_3$. Work-up as for the cyclopropyl analog gave 11.3 g of amide as a viscous oil. This was reduced in tetrahydrofuran (THF) with 3.5 g of $LiAlH_4$ to give 11.0 g of oil which was dissolved in 20 ml of ethanol, diluted with 15 ml of H_2O, and refrigerated to give 9.4 g of crude product. Two recrystallizations from aqueous ethanol gave 6.6 g, mp 81–84°.

Anal. Calcd for $C_{23}H_{29}N$: C, 86.46; H, 9.16; N, 4.38. Found: C, 86.63; H, 9.51; N, 4.44.

1,2,3,4,5,6-Hexahydro-*cis*-6,13-dimethyl-3-phenethyl-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—Reaction of 7.6 g of *cis*-norbase with 4.7 g of phenylacetyl chloride in the usual manner gave a quantitative yield of crude amide as an oil. This was reduced with 2 g of $LiAlH_4$ in THF to give 9.8 g of crude product as a yellow oil. The oil was dissolved in 50 ml of acetone and 3.5 g of oxalic acid dihydrate in 20 ml of acetone was added to give 10.1 g of oxalate melting at 220–225° dec. Recrystallization from 400 ml of 75% ethanol gave 7.1 g of white crystals, mp 232–234° dec, showing one spot on tlc. These were converted to the hydrochloride, mp 270–273°.

Anal. Calcd for $C_{25}H_{29}N \cdot HCl$: C, 79.66; H, 7.72; N, 3.57. Found: C, 79.34; H, 7.52; N, 3.56.

1,2,3,4,5,6-Hexahydro-*trans*-6,13-dimethyl-3-(3-methyl-2-butenyl)-2,6-methanonaphth[1,2-*d*]azocine Hydrochloride.—A mixture of 6.3 g of *trans*-norbase, 5.5 g of $NaHCO_3$, 55 ml of dimethylformamide, and 3.9 g of dimethylallyl bromide was stirred and refluxed for 4 hr, filtered, and concentrated *in vacuo*, and the residue was partitioned between H_2O and ethyl acetate. The ethyl acetate was dried, treated with charcoal, filtered, and concentrated to give 6.8 g of oil. This was converted to the hydrochloride, 5.0 g, mp 248–245° dec. Tlc indicated one impurity which was removed by recrystallization from ethanol; mp 266.8–268.0° dec (cor).

Anal. Calcd for $C_{23}H_{29}N \cdot HCl$: C, 77.61; H, 8.50; N, 3.94. Found: C, 77.55; H, 8.50; N, 4.00.

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Effect of Organic Compounds on Reproductive Processes. VII. Bis-N,N′-carbamoylaziridines

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Previous results from this laboratory have shown that certain N,N′-bis(aziridineacetyl)-α,ω-diamines were effective chemosterilants for houseflies.[1,2] Borkovec and Woods[3] reported that certain N-carbamoylaziri-

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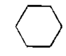
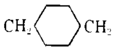
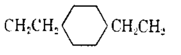
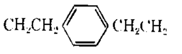
[1] W. A. Skinner, H. C. Tong, T. E. Shellenberger, and G. W. Newell, *J. Med. Chem.*, **8**, 647 (1965).

[2] W. A. Skinner, M. Cory, T. E. Shellenberger, and J. I. DeGraw, *ibid.*, **9**, 520 (1966).

[3] A. B. Borkovec and C. W. Woods, *ibid.*, **8**, 545 (1965).

TABLE I

N,N′-BISCARBAMOYLAZIRIDINES

Compd	R	Crystn solvent	Mp, °C[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	$(CH_2)_8$	Acetone	100–102[b]	55						
2	$(CH_2)_{10}$	Acetone	110–112	31	61.9	9.74	18.0	61.9	10.0	17.7
3		DMF	+300	22	57.1	7.99	22.2	56.8	8.09	21.9
4		DMF	171–173	41	60.0	8.63	20.0	59.8	8.54	19.7
5		THF	126.5–129	42	62.3	9.15	18.2	61.9	9.20	17.9
6		Acetone	132–138	30	61.3	6.61	20.4	61.5	6.56	20.5
7		Acetone	137.5–140	23	63.6	7.30	18.5	63.7	7.20	18.9

[a] Compounds polymerize upon slow heating; melting points were taken on a preheated Fisher-Johns melting point block. [b] H. Bestian, *Ann.*, **566**, 210 (1950), reported mp 104°.

TABLE II

EFFECTS OF COMPOUNDS ON REPRODUCTION OF HOUSEFLIES[a]

		% egg hatch[b]						
		Days of oviposition						
Compound	Wt % in feed	1	2	3	4	5	6	7
1	1.0	2	0	1	2	0	0	0
	0.1	11	4	1	24	10	8	15
	0.01	63	55	50	61	56	58	50
2	1.0	38	39	58	56	58	45	73
3	1.0	/	/	/	/	/	/	/
	0.1	/	3	0	0	0	0	/
4	1.0	/	/	/	/	/	/	/
5	0.1	—	70	59	48	—	73	78
	0.01	90	89	68	79	94	84	53
6	1.0	55	37	59	20	50	44	32
	0.1	60	51	43	68	41	52	60
7	1.0	60	58	40	—	70	62	74
	0.1	80	82	90	95	91	88	89

[a] Two hundred flies were used for each experiment. [b] Horizontal lines indicate that no data were obtained; slant lines indicate that no eggs were laid by the treated houseflies.

dines also were effective chemosterilants. Some of these compounds were effective chemosterilants for houseflies at 0.1% concentration in the diet while N,N′-*trans*-vinylenebis-1-aziridinecarboxamide was effective at 0.01% concentration. We were interested in preparing bis-N,N′-carbamoylaziridines from some of the carrier groups used in the aziridineacetyl series[1,2] and evaluating them as housefly chemosterilants.

Table I lists the chemical data of those compounds prepared by reaction of aziridine with the appropriate isocyanate. Table II lists the results of evaluating these compounds as housefly chemosterilants.

Experimental Section

General Method for N,N′-Biscarbamoylaziridines.—Isocyanates were prepared from the dicarboxylic acids by the procedure of Allen and Bell.[4] The crude isocyanates in a small amount of benzene were added after filtration to an ice-cold solution of 2 equiv of aziridine in benzene.[3] The reaction mixture was stirred for 1 hr at room temperature and filtered. Because the ureas tended to be heat sensitive, the recrystallizations were done with a minimum of heating.

1,4-Cyclohexanedipropionic Acid.—To a solution of 0.68 g (29.6 mg-atoms) of Na and 5.4 g (14.8 mmoles) of *trans*-1,4-diiodomethylcyclohexane,[5] mp 77–79°, was added 7.90 ml (44.4 mmoles) of diethyl malonate. The solution was heated at reflux for 7 hr. Ethanol was evaporated *in vacuo*, and the oily residue was partitioned between ether and H_2O. The ether was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was stirred at reflux with 25 ml of 6 *N* HCl for 16 hr, evaporated to dryness *in vacuo*, and heated at 190° for 0.5 hr. The residue was then partitioned between 0.1 *N* NaOH and ether, and the basic solution was acidified to pH 1 with 6 *N* NaOH and filtered. Recrystallization from acetone–H_2O yielded 1.7 g (50%) of white crystals, mp 235–237° (sealed, evacuated capillary).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.07; H, 8.64.

1,4-Cyclohexanediacetic Acid.—*trans*-1,4-Cyclohexanediacetic acid was prepared according to the procedure of Garcia and Wood,[6] mp 225–226° (lit.[6] 226–227°).

***p*-Phenylenedipropionic Acid.**—*p*-Phenylenediacrylic acid (10.0 g, 45.9 mmoles), 250 ml of tetrahydrofuran (THF), and 3 scoops of Raney Ni W-2 (4.2 kg/cm², 60°) absorbed half the theoretical H_2 in 24 hr. After addition of 1.0 g of PtO_2 in 5 ml of THF, hydrogenation (same conditions) went to completion. The catalyst was filtered, and the solution was evaporated to dryness *in vacuo*. The residue was recrystallized from 100 ml of THF to yield 6.8 g (67%) of white crystals, mp 222–225° (lit.[7] 228–230°).

Biological Methods.—All the aziridine derivatives listed in Table I were evaluated in our colony of houseflies (*Musca domestica* L.). The method used was that previously reported.[1] All compounds were mixed dry in the feed.

Discussion

The most active compounds of this series appear to be **1**, **3**, and **4**. It is interesting that, as in the case of the aziridineacetyl derivatives previously reported,[1,2] the C_8 aliphatic compound (**1**) is more active than the C_{10} compound (**2**). This again emphasizes the importance of spacing between the two alkylating functions. However, in contrast to the finding in the aziridineacetyl series, the xylylenediamine derivative **6** is not very active in this carbamoylaziridine series. Compounds **3** and **4** would appear worthy of further study as chemosterilants, provided mammalian toxicity is not too great.

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(4) C. F. H. Allen and A. Bell, *Org. Syn.*, **24**, 94 (1944).

(5) C. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 404 (1953).

(6) P. Garcia and J. H. Wood, *J. Org. Chem.*, **26**, 4167 (1961).

(7) S. Malinowski and S. Benhenick, *Roczniki Chem.*, **27**, 379 (1953); *Chem. Abstr.*, **49**, 1035a (1955).

Toxicity data in mice with six daily intraperitoneal injections show that **7** killed two of three mice at 2.5 mg/kg, **1** killed three of three mice at 2.5 mg/kg, and **6** killed three of three mice at 5 mg/kg. These are, thus, fairly toxic compunds, considerably more so than the corresponding aziridineacetyl derivatives.[8]

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A Synthesis of 11β-Hydroxyestrone and Related 16- and 17-Hydroxyestratrienes

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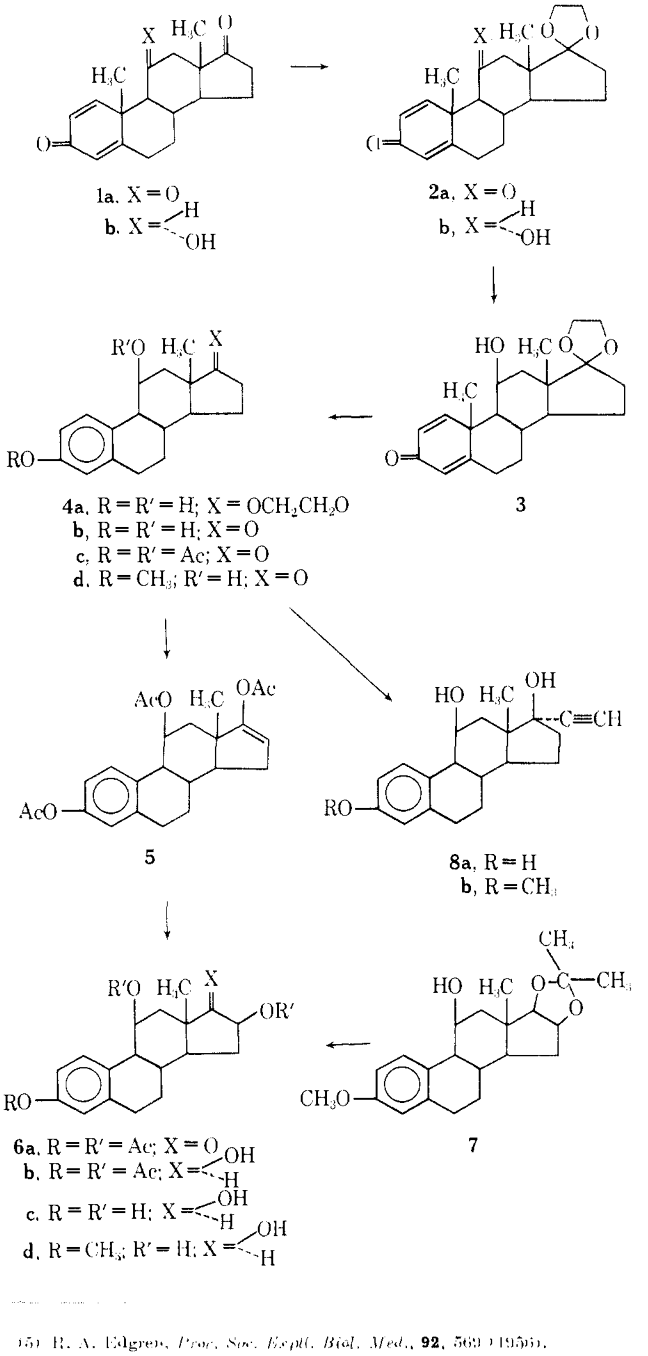
3,11-Dihydroxyestra-1,3,5(10)-trienes have been previously obtained from steroidal 11-oxygenated 1,4-dien-3-ones by pyrolysis in low yield.[1] A new and convenient synthesis of 11β-hydroxyestrone (**4b**) from androsta-14-diene-3,17-dione (**1a**) is now reported. The availability of 11β-hydroxyestrone made it suitable for conversion to derivatives which may be of biological interest, among them the 16- and 17-hydroxylated estratrienes.[2]

The recent discovery of the reductive aromatization of steroidal 1,4-dien-3-ones[3] was applied to the 11-hydroxydienones **2b** and **3**. When **1a** or **1b** was refluxed with *p*-toluenesulfonic acid and ethylene glycol in benzene, **2a** and **2b** were obtained, respectively. Selective reduction of the C-11 ketone **2a** with lithium tri-*t*-butoxyaluminum hydride yielded **3**. Reductive aromatization of **3** with loss of the angular methyl group to **4a** proceeded in yields up to 72%. Hydrolysis of **4a** gave **4b**. In contrast to the reductive aromatization of **3**, the 11α-hydroxydienone **2b** was reduced to a product in which the rupture of the bond between carbon atoms 9 and 10 had probably occurred. Evidence for this conclusion was obtained from the nmr spectrum of the crude product which exhibited peaks for a methyl group and three hydrogens on a benzene ring.

When **4b** was heated with acetic anhydride and pyridine, the diacetate **4c** was obtained which upon treatment with *p*-toluenesulfonic acid and isopropenyl acetate yielded **5**. The enol acetate **5** was converted with lead tetraacetate in acetic acid to a mixture of 16-acetoxy 17-ketones in which the 16β isomer **6a** was preponderant.[4] Reduction of **6a** with lithium tri-*t*-butoxyaluminum hydride followed by hydrolysis with aqueous potassium hydroxide gave **6c**. Evidence for the *cis* configuration of the 16,17-glycol **6c** was furnished when it was monomethylated to **6d** which then was converted to the acetonide derivative **7**. Ethynylation of **4b** and **4d** with lithium acetylide–ethylenediamine complex in dimethyl sulfoxide yielded the 11β-hydroxyethynylestradiol **8a** and its 3-methyl ether **8b**, respectively.

Biology.—Compounds **6c** and **8a** had 0.05 and 5% the activity of estrone, respectively, when administered by injection in the mouse uterine growth assay.[5] Compound **8a** produced no decidual cell formation[6] in the immature female rabbit when treated by injection at 10 mg/day.[7]



1a, X = O

b, X = $<^{\text{H}}_{\text{OH}}$

2a, X = O

b, X = $<^{\text{H}}_{\text{OH}}$

3

4a, R = R' = H; X = OCH$_2$CH$_2$O

b, R = R' = H; X = O

c, R = R' = Ac; X = O

d, R = CH$_3$; R' = H; X = O

5

8a, R = H

b, R = CH$_3$

6a, R = R' = Ac; X = O

b, R = R' = Ac; X = $<^{\text{OH}}_{\text{H}}$

c, R = R' = H; X = $<^{\text{OH}}_{\text{H}}$

d, R = CH$_3$; R' = H; X = $<^{\text{OH}}_{\text{H}}$

7

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(1) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2220 (1958).

(2) Steroids hydroxylated at C-11 or -16 may be metabolites of the natural or synthetic estrogens. See R. I. Dorfman and F. Ungar, "Metabolism of Steroid Hormones," Academic Press Inc., New York, N. Y., 1965.

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(7) The author is indebted to Dr. E. F. Nutting and Mr. R. Bergstrom of the Division of Biological Research, G. D. Searle & Co., for the biological data reported herein.