The ketone III is converted into 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa) with either potassium acetylide or the lithium acetylide–ethylenediamine complex. When heated with acetic anhydride and pyridine, IVa gives the acetate IVb, while successive carboxylation and hydrogenation[1a] transform IVa into the spirolactone, 3-(17β-hydroxy-1,4-dimethylestra-1,3,5(10)-trien-17α-yl)propionic acid lactone (V).

Experimental Section[6]

1,4-Dimethylestra-1,3,5(10)-trien-17-one (III).[4]—To a stirred solution of 20 ml of 3 *M* methylmagnesium bromide in diethyl ether and 200 ml of anhydrous ether was added a mixture of 10 g of androsta-1,4-diene-3,17-dione 17-ethylene ketal[7] in 700 ml of anhydrous ether. The reaction mixture was stirred and heated under reflux for 2.5 hr. Then it was cooled in an ice bath and decomposed with a saturated solution of NH_4Cl. The ether phase was separated, washed successively with water and a saturated solution of NaCl, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford a viscous oil. The oil was treated with a solution of 9 ml of 6 *N* HCl in 90 ml of 95% ethanol. The mixture was stirred at room temperature for 0.5 hr. Then it was diluted with water and extracted with ether. The ether extract was separated and worked up as previously described. The resultant viscous oil was chromatographed on 700 g of silica gel. Elution of the column with benzene gave 3.3 g of a colorless crystalline product, which melted at 126–127° after crystallization from ether–pentane (lit.[4] 126–128°). It proved identical with an authentic sample of IV prepared by the CrO_3 oxidation[4] of 1,4-dimethylestra-1,3,5(10)-trien-17β-ol (III)[3a] obtained from either 17β-hydroxyandrosta-1,4-dien-3-one (Ia) or its acetate (Ib).

17α-Ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa). A.—Acetylene was passed for 1 hr into a solution of 15 g of potassium *t*-butoxide in 200 ml of *t*-butyl alcohol and 100 ml of toluene, stirred, and maintained in an ice bath. A solution of 1.6 g of III in 40 ml of toluene was then added as acetylene was still being passed into the solution. After 4 hr, passage of acetylene was stopped. The reaction mixture was stirred for an additional 12 hr during which time it was permitted to warm to room temperature. The reaction mixture was then diluted with a large volume of a saturated solution of NH_4Cl. The organic phase was separated, washed with water, and distilled to dryness under reduced pressure. The residue was chromatographed on 80 g of silica gel. Elution with 2% ethyl acetate in benzene gave Va, which was crystallized from ether–pentane, mp 170.5–172°, yield 0.31 g. The melting point was raised to 174–174.5° on recrystallization from ether–pentane; λ^{KBr} 3425, 3311, 3289, 801 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.87; H, 9.22.

B.—A mixture of 1.36 g of III, 2.7 g of lithium acetylide–ethylenediamine,[8] and 100 ml of tetrahydrofuran (freshly distilled from methylmagnesium bromide) was stirred at room temperature for 2 hr. The reaction mixture was decomposed with a dilute solution of NH_4Cl and then extracted with ether. The ether extract was washed successively with water and a saturated solution of NaCl, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford a viscous orange-red oil. The oil was chromatographed on 150 g of silica gel. Elution with benzene, followed by crystallization of the solid product from ether–pentane, afforded 0.54 g of IVa, mp 171–171.5°, which was identical with that obtained by procedure A. From the mother liquor an additional 0.12 g of IVa, mp 164.5–167.5°, was obtained.

17α-Ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol Acetate (IVb).—A solution of 0.78 g of IVa, 6 ml of pyridine, and 8 ml of acetic anhydride was maintained at 95° for 18 hr after which time it was concentrated to about 2 ml by distillation under reduced pressure. The residue was diluted with ice water and extracted with ether. The ether extract was washed successively with a 5% solution of $NaHCO_3$ and water, dried (Na_2SO_4), and distilled to dryness under reduced pressure. The residual viscous oil was chromatographed on 80 g of silica gel. Elution with benzene gave a colorless viscous oil. This was evaporatively distilled at 180° (0.1 mm) to afford IVb as a colorless amorphous product, λ^{KBr} 3311, 2119, 1761, 1592, 1250, 1241, 1229, 806 cm^{-1}. Thin layer chromatography indicated that the product was homogeneous.

Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.17; H, 8.65.

3-(17β-Hydroxy-1,4-dimethylestra-1,3,5(10)-trien-17α-yl)propionic Acid Lactone (V).—To a stirred solution of 15 ml of 3 *M* methylmagnesium bromide in diethyl ether and 25 ml of tetrahydrofuran (THF) was added over a period of 10 min a solution of 2.4 g of IVa in 30 ml of THF. The reaction mixture was distilled to remove the diethyl ether. Then it was stirred and heated under reflux under N_2 for 15 hr. The cooled reaction mixture was stirred for an additional 22 hr while CO_2 was continuously passed into it. An ice-cold, dilute solution of H_2SO_4 was added. The resultant solid was collected, washed well with water, and dried, mp 105–110°. A solution of the solid (2.7 g) and 0.83 g of triethylamine in 100 ml of 95% ethanol was hydrogenated over 0.3 g of 5% Pd–C at room temperature and atmospheric pressure. After the calculated amount of hydrogen was absorbed, hydrogenation was stopped. The filtered solution was distilled to dryness under reduced pressure. The residue was triturated with dilute HCl to afford a colorless crystalline product. The product was collected, washed well with water, and dried. Crystallization from methanol–water gave 1.65 g of V; mp 200–202.5°; λ^{KBr} 1792, 1595, 804 cm^{-1}; $[\alpha]^{20}D$ +8.9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.74; H, 8.85.

(6) Melting points were taken on a Fisher-Johns melting block and are corrected.

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Synthesis and Pharmacological Evaluation of α-Substituted 1-Naphthylacetic Acids

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Continuing our investigation on the pharmacological properties of α,α-disubstituted 1-naphthylacetonitriles and 1-naphthylacetamides,[1] we have prepared 21 α-substituted 1-naphthylacetic acids for pharmacological screening, including studies of acute toxicity and antiinflammatory, antipyretic, analgesic, diuretic, choleretic, and hypoglycemic action, as well as the *in vitro* antibacterial and antifungal activities.

The monosubstituted acids were prepared by hydrolysis of the nitriles with dilute sulfuric acid (see Experimental Section, methods A and B). This procedure failed to give the disubstituted acids, only the corresponding amides being obtained as previously reported.[1b] However, these acids were easily prepared by reaction of the amides with isoamyl nitrite in glacial acetic acid, in the presence of HCl (method C), as described for α-alkyl-substituted 1-naphthylacetic acids.[2] All the acids were isolated and identified as the hydrochlorides (Table I).

The results of the pharmacological screening are reported in Table II. Compared with the corresponding

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TABLE I: α-SUBSTITUTED 1-NAPHTHYLACETIC ACIDS

Compd	R	R′	Method	Yield, %[a]	Mp, °C dec[b]	Crystn solvent[c]	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
I	H	$(CH_3)_2N(CH_2)_2$	A	82	226–227	A–E	$C_{16}H_{19}NO_2 \cdot HCl$	65.41	6.86	12.07	4.77	65.30	6.91	11.83	4.79
II	CH_3	$(CH_3)_2N(CH_2)_2$	C	88	257	95% A	$C_{17}H_{21}NO_2 \cdot HCl$	66.33	7.20	11.52	4.45	65.95	7.11	11.41	4.38
III	C_2H_5	$(CH_3)_2N(CH_2)_2$	C	96	236–237	A–L	$C_{18}H_{23}NO_2 \cdot HCl$	67.17	7.52	11.02	4.35	66.95	7.51	10.94	4.29
IV	i-C_3H_7	$(CH_3)_2N(CH_2)_2$	C	90	227–228	A–L	$C_{19}H_{25}NO_2 \cdot HCl$	67.93	7.80	10.52	4.17	68.15	7.79	10.32	4.08
V	sec-C_4H_9	$(CH_3)_2N(CH_2)_2$	C	87	208–209	I	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	8.07	10.13	4.00	68.83	7.93	9.96	4.04
VI	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	C	83	227.5–229	A–L	$C_{20}H_{28}N_2O_2 \cdot 2HCl$	59.84	7.53	17.67	6.98	59.20	7.67	17.70	6.86
VII	i-C_3H_7	$CH_3(C_2H_5)N(CH_2)_2$	C	86	190–192	A–E	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	8.07	10.13	4.00	68.15	8.14	10.01	3.92
VIII	H	$(C_2H_5)_2N(CH_2)_2$	A	93	207–208	A–I	$C_{18}H_{23}NO_2 \cdot HCl$	67.17	7.52	11.02	4.35	67.13	7.59	10.92	4.29
IX	i-C_3H_7	$(C_2H_5)_2N(CH_2)_2$	C	78	195–196	I	$C_{21}H_{29}NO_2 \cdot HCl$	69.31	8.31	9.74	3.85	69.84	8.38	9.80	3.93
X	H	[d]	B	77	197–199	I	$C_{19}H_{23}NO_2 \cdot HCl$	68.35	7.24	10.62	4.19	68.21	7.22	10.51	4.06
XI	CH_3	[d]	C	95	255–256	95% A	$C_{20}H_{25}NO_2 \cdot HCl$	69.05	7.53	10.19	4.03	68.72	7.43	10.17	4.10
XII	C_2H_5	[d]	C	82	246–247	A	$C_{21}H_{27}NO_2 \cdot HCl$	69.69	7.80	9.80	3.87	69.65	7.73	9.68	3.93
XIII	i-C_3H_7	[d]	C	84	214–215	A–L	$C_{22}H_{29}NO_2 \cdot HCl$	70.29	8.05	9.43	3.72	70.39	8.06	9.44	3.66
XIV	sec-C_4H_9	[d]	C	91	218–220	A	$C_{23}H_{31}NO_2 \cdot HCl$	70.84	8.27	9.09	3.59	70.04	8.10	8.83	3.48
XV	[d]	[d]	C	88	214.5–216	A–L	$C_{26}H_{36}N_2O_2 \cdot 2HCl$	64.85	7.96	14.73	5.82	63.90	7.94	14.42	5.72
XVI	H	[e]	A	97	261–262	90% A	$C_{18}H_{21}NO_3 \cdot HCl$	64.37	6.60	10.56	4.17	64.16	6.64	10.23	4.15
XVII	CH_3	[e]	C	95	245–246	95% A	$C_{19}H_{23}NO_3 \cdot HCl$	65.22	6.91	10.14	4.00	65.90	7.09	10.15	4.10
XVIII	C_2H_5	[e]	C	95	244–245	90% A	$C_{20}H_{25}NO_3 \cdot HCl$	66.01	7.20	9.74	3.85	65.70	7.12	9.56	3.88
XIX	i-C_3H_7	[e]	C	77	203–204	A–L	$C_{21}H_{27}NO_3 \cdot HCl$	66.74	7.47	9.38	3.71	66.11	7.62	9.19	3.76
XX	sec-C_4H_9	[e]	C	93	222	A	$C_{22}H_{29}NO_3 \cdot HCl$	67.41	7.72	9.05	3.57	66.88	7.84	9.01	3.49
XXI	[e]	[e]	C	94	221–223	A	$C_{23}H_{32}N_2O_4 \cdot 2HCl$	59.38	7.06	14.61	5.77	58.85	7.14	14.35	5.72

[a] Crude product. [b] Hydrochlorides. [c] A = ethanol, E = ether, I = 2-propanol, L = ligroin (bp 75–120°). [d] β-Piperidinoethyl. [e] β-Morpholinoethyl.

I–XXI (see Table I)

nitriles and amides,[1a,b] the title compounds displayed a somewhat lower but still noticeable antiinflammatory activity, particularly considering their lower toxicity; from this point of view, XI (α-methyl-α-2-piperidinoethyl-1-naphthylacetic acid) was found to be of particular interest. Nevertheless, the good antiinflammatory activity was not accompanied by an equally good analgesic action; this was distinctly inferior to that of the parent compounds. The whole series revealed a significant although short-lasting antipyretic action; some of the compounds were more active than phenylbutazone. The diuretic action of all the compounds was low.

Among the compounds investigated for choleresis, XVI (α-2-morpholinoethyl-), XVIII (α-ethyl-α-2-morpholinoethyl-), and especially XVII (α-methyl-α-2-morpholinoethyl-1-naphthylacetic acid) greatly increased the bile flow. Of the compounds studied in the hypoglycemic test, VII (α-isopropyl-α-2-methylethylaminoethyl-) and IX (α-isopropyl-α-2-diethylaminoethyl-1-naphthylacetic acid) displayed a marked activity. None of the compounds showed significant antibacterial and antifungal activities *in vitro*. Thus the most interesting points are the choleretic and hypoglycemic properties revealed by some compounds of this series.

Experimental Section[3]

Chemistry.—The intermediate nitriles and amides were prepared as recently reported.[1a,b] The title compounds were obtained by three different methods which are well illustrated by the following methods A, B, and C. They are listed in Table I, along with yields, physical constants, and analytical data.

Method A. α-(2-Morpholinoethyl)-1-naphthylacetic Acid Hydrochloride (XVI).—α-(2-Morpholinoethyl)-1-naphthylacetonitrile (50 g, 0.176 mole) was hydrolyzed by refluxing for 2 hr with a 1:1:1 mixture of concentrated H_2SO_4, glacial acetic acid, and water (195 ml). The reaction mixture was cooled to room temperature, diluted with water, and washed with ether. The aqueous layer was made alkaline with 30% NaOH, washed twice with ether and acidified to pH 1 with 20% HCl. The acid solution was evaporated to dryness under reduced pressure, and the residue was extracted four times with boiling ethanol (800 ml). The combined extracts were evaporated to dryness and the residue was crystallized from 90% ethanol, giving colorless crystals, mp 261–262°.

Method B. α-(2-Piperidinoethyl)-1-naphthylacetic Acid Hydrochloride (X).—α-(2-Piperidinoethyl)-1-naphthylacetonitrile (40 g, 0.144 mole) was first hydrolyzed as described in method A. The reaction mixture was then cooled, diluted with water, washed with ether, and made alkaline with 50% NaOH. An oil separated which was washed with ether, and then concentrated HCl was added to pH 1. The oily layer was again separated and dissolved in 2-propanol, the solution was dried ($CaCl_2$), and ether was then added. The tarry precipitate obtained was crystallized from 2-propanol, giving a colorless crystalline product, mp 197–199°.

Method C. α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetic Acid Hydrochloride (IV).—Hydrogen chloride was slowly bubbled for 1.5 hr, at room temperature, through a cooled solution of α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthyl-

(3) Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

TABLE II

PHARMACOLOGICAL SCREENING RESULTS

Compd	Approx LD_{50} (mouse), mg/kg ip	Analgesic act. (mouse) Increase of reaction time, %[a]	mg/kg ip	Antiinflammatory activity (rat) Inhibition of edema, %[b]	mg/kg ip	Antipyretic act. (rat) Max temp decrease, °C[c]	mg/kg ip	Diuretic activity (rat) Test vol[c,f] control vol	mg/kg po	Choleretic activity (rat) Increase of bile flow, %[d] 1 hr	2 hr	mg/kg[e] id	Hypoglycemic activity (rat) Blood sugar decrease, %[f]	mg/kg po
I	1120–1230	14	200	30	200	2.2	200	Inactive	50	32	18	73	Inactive	100
II	560–630	21	100	13	100	1.4	100	1.15	50					
III	1090–1210	37	100	15	100	2.2	100	Inactive	50				14	50
IV	>800	59	200	25	200	2.2	200	1.29	50					
V	540–610	54	200	17	200	2.4	200	1.19	50				Inactive	100
VI	580–620	8	100	22	100	1.4	100	1.15	50				13	100
VII	510–590	38	200	47	200	3.2	200	1.12	50				35	50
VIII	290–320	58	200	37	200	3.1	200	Inactive	50	Inactive	Inactive	80		
IX	550–620	10	200	Inactive	200	3.4	200	Inactive	50				38	50
X	45–70	28	25	26	25	0.8	25	1.30	50	Inactive	36	83	Inactive	100
XI	1100–1260	12	100	50	100	2.9	100	Inactive	50					
XII	570–640	23	200	Inactive	200	2.4	200	1.27	50					
XIII	780–820	34	200	37	200	2.7	200	1.13	50				Inactive	50
XIV	590–650	50	200	30	200	3.3	200	1.14	50				Inactive	100
XV	280–310	14	50	Inactive	50	0.9	50	Inactive	50				Inactive	100
XVI	1140–1220	16	200	45	200	2.1	200	Inactive	50	97	39	83	11	100
XVII	410–450	34	100	Inactive	100	1.3	50	1.18	50	134	131	87		
XVIII	390–410	36	50	38	50	0.7	100	Inactive	50	92	78	90		
XIX	1170–1250	13	100	Inactive	100	1.6	100	Inactive	50					
XX	590–630	28	100	18	100	2.7	100	Inactive	50				12	100
XXI	>1600	9	100	Inactive	100	1.7	100	Inactive	50	28	43	120	Inactive	100
Morphine·HCl		67	5											
Phenylbutazone		61	100	18	100	1.6	100							
Hydrochlorothiazide								1.56	6.25					
Dehydrocholic acid										92	42	100		
Chlorpropamide													37	50

[a] Hot plate test, 1 hr after treatment. [b] Formalin-induced edema, 2 hr after treatment. [c] 5 hr of observation. [d] Values at 1 and 2 hr after treatment. [e] Equimolar doses. [f] Values referred to basal glycemia, 2 hr after treatment.

acetamide (40 g, 0.134 mole) in glacial acetic acid (200 ml). Freshly distilled isoamyl nitrite (50 ml) was then added over 2 hr with stirring. The bright red solution was kept at room temperature for additional 2 hr, and then heated at 100° for 8 hr. The solvent was distilled from the reaction mixture at 50° under reduced pressure, and then ether was added to the residue, giving a solid product which, on crystallization from ethanol–ligroin (bp 75–120°), gave colorless crystals, mp 227–228°.

Pharmacology.—The acute toxicity, and antiinflammatory, analgesic, and diuretic activities were investigated according to the techniques previously described.[1a] The antipyretic action was studied in rats made pyretic by brewer's yeast, according to Smith and Hambourger.[4] The activity on the choleresis was investigated in rats, using the biliary fistula technique of Marazzi-Uberti and Turba.[5] The hypoglycemic action was measured in rats, according to the procedure described by Ceriotti.[6] The antibacterial and antifungal activities were measured against *Micrococcus pyogenes var. aureus* ATCC 6538 P, *Bacillus subtilis* ATCC 6633, *Escherichia coli* McLeod ATCC 10,536, *Salmonella typhi* T 30 Roma M 507, and *Candida albicans* ATCC 10,231, using the serial dilution technique.[7] All compounds were administered as the hydrochlorides in aqueous solution. Morphine, phenylbutazone, hydrochlorothiazide, dehydrocholic acid, and chlorpropamide were used as standards for comparing the analgesic, antiinflammatory–antipyretic, diuretic, choleretic, and hypoglycemic activities, respectively.

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Effect of Organic Compounds on Reproductive Processes. II. Alkylating Agents Derived from Various α,ω-Alkylenediols

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A program of synthesis of alkylating agents having related carrier moieties but with a variety of alkylating functions has been under way in our laboratories. These compounds are being evaluated for their effect on reproduction in the housefly (*Musca domestia* L.), mice, and Japanese quail. Previous studies have shown that N,N′-bis(aziridinylacetyl)-1,8-octamethylenediamine[1] inhibits reproduction in the housefly at 1 and 0.1% concentration when added to their feed. It was of interest to see whether similar compounds derived from α,ω-alkanediols would also affect their reproduction.

The compounds synthesized (**2**–**21**) are shown in Table I. The bisbromoacetyl esters (**2**, **6**, **10**, and **14**) were best prepared by the addition of diol to chilled bromoacetyl bromide. The iodo derivatives (**3**, **7**, **11**, and **15**) were prepared from the bromo compounds using NaI in acetone. The aziridinyl derivatives (**4**, **8**, and **12**) were derived from the bromo compounds by the addi-

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