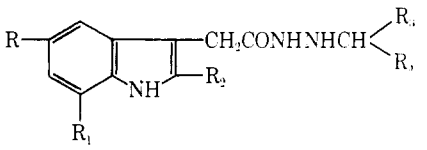
TABLE IV
SUBSTITUTED INDOLE N-ISOPROPYLHYDRAZIDES



R	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Formula[b]	MAO inhib,[c] %
H	H	CH_3	CH_3	CH_3	85	50	$C_{14}H_{19}N_3O$[d]	50.0, 49.0 (49.5)
H	H	CH_3	CH_3	C_2H_5	70	50	$C_{15}H_{21}N_3O$	42.3, 41.5 (41.9)
CH_3	H	CH_3	CH_3	CH_3	148	65	$C_{15}H_{21}N_3O$	50.0, 50.0 (50.0)
CH_3	H	CH_3	CH_3	C_2H_5	105	70	$C_{16}H_{23}N_3O$	42.0, 40.0 (41.0)
H	CH_3	CH_3	CH_3	CH_3	145	60	$C_{15}H_{21}N_3O$	50.0, 48.4 (49.2)
H	CH_3	CH_3	CH_3	C_2H_5	100	65	$C_{16}H_{23}N_3O$	48.0, 47.0 (47.5)
CH_3O	H	CH_3	CH_3	CH_3	110	60	$C_{15}H_{21}N_3O_2$	50.0, 48.0 (49.0)
CH_3O	H	CH_3	CH_3	C_2H_5	80	65	$C_{16}H_{23}N_3O_2$[e]	48.0, 50.0 (49.0)

[a] Melting points were taken in open capillary tubes and are graphically corrected. [b] The compounds were analyzed for C, H, N. [c] Vessel contents and the assay procedures are as indicated in the text. Each experiment was done in duplicate. Figures in the parentheses indicate mean values. [d] *Anal.* C: calcd, 68.46; found, 69.15. [e] *Anal.* C: calcd, 66.43; found, 65.92.

solvent was removed under reduced pressure. The hydrazines were crystallized by dissolving in a minimum amount of EtOH and adding petroleum ether (bp 40–60°) to incipient turbidity. The crude product was recrystallized from the appropriate solvent (see Table IV).

Determination of Monoamine Oxidase Activity.—The spectrophotofluorometric method of Kramel[11] was used for the determination of the MAO activity of rat liver homogenate using kynuramine as the substrate. The 4-hydroxyquinoline, formed during oxidative deamination of kynuramine, was measured fluorometrically in an Aminco Bowman spectrophotofluorometer using activating light of 315 mμ and measuring fluorescence at the maximum of 380 mμ.

Male adult rats weighing approximately 150–200 g were killed by decapitation. Livers were quickly removed and homogenized in ice-cold 0.25 *M* sucrose with the help of Potter-Elvehjem homogenizer. The reaction mixture consisted of phosphate buffer, 0.5 ml (pH 7.5, 0.5 *M*), 0.5 ml of kynuramine (100 μg), and 0.5 ml of liver homogenate (corresponding to 5 mg of wet weight of the tissue). The MAO activity of the liver homogenate was determined by incubation for 30 min at 37° in air. The various inhibitors, used at the final concentration of 1×10^{-3} *M*, were added to the liver homogenate and incubated for 10 min before the addition of kynuramine. The mixture was further incubated for 30 min. The reaction was stopped by the addition of 2 ml of 10% TCA and the precipitated proteins were removed by centrifugation. Suitable aliquots of the supernatant were taken in 1 *N* NaOH solution and were assayed for 4-hydroxyquinoline. Increase in the optical density provided a direct measurement of the 4-hydroxyquinoline which was taken as an index of the enzyme activity. The per cent inhibition was calculated from the decrease observed in the optical density.

Results and Discussion

The MAO inhibitory activities of substituted indole N-isopropylhydrazides using rat liver homogenate during oxidative deamination of kynuramine are shown in Table IV. The various indole hydrazides shown in Table III were found to be devoid of enzyme inhibitory properties. Reduction of some of these hydrazides (Table III) led to the corresponding hydrazines (Table IV) which, however, exhibited MAO inhibitory properties. Similar results have been reported earlier by Zeller[12] where no inhibition of the enzyme MAO could be observed with isoniazid, as compared to iproniazid. All the substituted indoleacylhydrazines were equally effective in inhibiting the enzyme activity since the degree of inhibition produced by these compounds was fairly constant. Substitution in the indole nucleus or in the hydrazine side chain was found to have no specific effect on their ability to inhibit rat liver MAO. At present it is difficult to evaluate a structure–activity relationship of these substituted hydrazines. It is presumed that investigations dealing with the determination of the substrate specificity and the inhibitory effects of these compounds during oxidation of tryptamines could provide better knowledge regarding their structure–activity relationship as MAO inhibitors.

Acknowledgments.—The authors wish to express their thanks to Dr. J. P. Barthwal and Dr. K. Kishor for their advice and encouragement, and to Dr. M. L. Dhar and Dr. Nitya Anand of the Central Drug Research Institute, Lucknow, for providing microanalysis facilities. A generous gift of Aminco Bowman spectrophotofluorometer by the Rockefeller Foundation and the research chemicals from the Riker Laboratories, Northridge, California, is gratefully acknowledged.

(11) M. Kramel, *Biochem. Pharmacol.*, **14**, 1684 (1965).

(12) E. A. Zeller in "Metabolic Inhibitors: A Comprehensive Treatise," Vol. II, R. M. Hochster and J. H. Quastel, Ed., Academic Press, New York, N. Y., 1963, p 53.

The Synthesis and Pharmacological Properties of a Series of 2-Substituted Aminomethyl-1,4-benzodioxanes

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Since Fourneau and Bovet[2] first described benzodioxanes as epinephrine antagonists a large number of related compounds possessing similar properties have been reported. Bovet and Simon[3] investigated the adrenolytic and sympatholytic properties of a series of aminomethylbenzodioxanes and noted the effect of these compounds on the CNS. The preparation of N,N'-ethylenediamine and piperazine derivatives structurally related to 2-diethylaminomethyl-1,4-benzodioxane (prosympal) and 2-(1-piperidylmethyl)-1,4-benzodioxane (piperoxan) have been described[4] and the pharmacological properties of some of these compounds

(1) To whom enquiries should be addressed.

(2) (a) E. Fourneau and D. Bovet, *Arch. Intern. Pharmacodyn.*, **46**, 179 (1933); (b) D. Bovet and F. Bovet-Nitti, "Structure et Activité Pharmacodynamique des Médicaments du Système Nerveaux Végétatif," Verlag S. Karger, Basel, 1948, pp 241–271.

(3) D. Bovet and A. Simon, *Arch. Intern. Pharmacodyn.*, **55**, 15 (1937).

(4) (a) A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5089 (1954); (b) *Ibid.*, **76**, 5091 (1954).

TABLE I

PHYSICAL AND ANALYTICAL DATA OF NEW 2-SUBSTITUTED AMINOMETHYL-1,4-BENZODIOXANES

No.	n	R	Bp of base, °C (mm)	Base or HCl: Formula	Base or HCl: Mp, °C	Crystn solvent	Analyses[c]
1	2	CH_3	152–156 (2.50)	$C_{12}H_{18}ClNO_3$	148–150	*i*-PrOH	C, H, Cl
2	2	$CH_3OCH_2CH_2$	180–186 (1.50)	$C_{14}H_{22}ClNO_4$	102–104	*i*-PrOH	C, H, Cl
3	2	$CH_3(OCH_2CH_2)_2$	188 (0.50)	$C_{16}H_{25}NO_5$	Oil		C, H, N
4	2	C_6H_5	204–208 (1.25)	$C_{17}H_{20}ClNO_3$	223–224	H_2O	C, H, Cl
5	2	*o*-$CH_3C_6H_4$	222–228 (2.00)	$C_{18}H_{22}ClNO_3$	169–171	EtOH	C, H, Cl
6	2	2,6-$(CH_3)_2C_6H_3$	214–218 (1.25)	$C_{19}H_{24}ClNO_3$	157–158	*i*-PrOH	C, H, Cl
7[a]	2	*o*-$CH_3OC_6H_4$	220–222 (1.00)	$C_{18}H_{21}NO_4$	60–62	PE[b]	C, H, N
8	2	*m*-$CH_3OC_6H_4$	232–238 (1.00)	$C_{18}H_{22}ClNO_4$	160–162	*i*-PrOH	C, H, Cl
9	2	*p*-$CH_3OC_6H_4$	224–228 (1.00)	$C_{18}H_{21}NO_4$	66	PE[b]	C, H, N
10	2	2,6-$(CH_3O)_2C_6H_3$	234–238 (1.25)	$C_{19}H_{24}ClNO_5$	155–157	*i*-PrOH	C, H, Cl
11	2	$C_6H_5CH_2$	216–222 (2.00)	$C_{18}H_{22}ClNO_3$	142–144	*i*-PrOH	C, H, Cl
12	3	$CH_3OCH_2CH_2$	180–186 (1.00)	$C_{15}H_{24}ClNO_4$	141–143	*i*-PrOH	C, H, Cl
13	3	C_6H_5	212–218 (1.50)	$C_{18}H_{22}ClNO_3$	184–186	*i*-PrOH	C, H, Cl
14	3	2,6-$(CH_3O)_2C_6H_3$	238–242 (0.75)	$C_{20}H_{26}ClNO_5$	145–146	*i*-PrOH	C, H, Cl
15	3	$C_6H_5CH_2$	213–218 (1.00)	$C_{19}H_{24}ClNO_3$	124–126	*i*-PrOH	C, H, Cl
16	4	C_6H_5	226–231 (2.00)	$C_{19}H_{24}ClNO_3$	154–156	EtOH	C, H, Cl
17	4	$C_6H_5CH_2$	228–234 (1.50)	$C_{20}H_{26}ClNO_3$	133–135	*i*-PrOH	C, H, Cl

[a] During the course of the work described in this paper the preparation of the hydrated hydrochloride of **7** was given as example 4 by British Patent 1,054,104 (1967). [b] PE = petroleum ether (bp 60–80°). [c] Analyses by Weiler and Strauss. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

have been reported.[5] More recently, Misiti, *et al.*,[6] prepared and studied the pharmacological activities of 2-(1-aminoethyl)-1,4-benzodioxanes and compared them with the corresponding 2-aminoethyl analogs. In this paper we are reporting a new series of 2-aminomethyl-1,4-benzodioxanes in which different substituents are attached to nitrogen.

Experimental Section

The new compounds are listed in Table I. They were prepared by treating 2-aminomethyl- or 2-chloromethyl-1,4-benzodioxane with the required halogeno- or amino-substituted intermediates. 2-Aminomethyl-1,4-benzodioxane was prepared by treating 2-chloromethyl-1,4-benzodioxane with potassium phthalimide in refluxing DMF and then treating the resultant 2-phthalimidomethyl-1,4-benzodioxane with N_2H_4. The majority of the desired halogeno intermediates were synthesized from the corresponding hydroxy derivatives *via* the action of $SOCl_2$ in pyridine. The hydroxy derivatives, if not readily available, were prepared by one of two methods: reaction between (a) ethylene carbonate and a potassium phenoxide, (b) benzyl chloride and a monosodium salt of a glycol.[7] The 3-(2,6-dimethoxyphenoxy)-propyl chloride and 4,7-dioxaoctyl chloride were obtained by reaction between 3-chloropropyl bromide and potassium 2,6-dimethoxyphenoxide and sodium 2-methoxyethoxide, respectively.

The general synthetic method used for the compounds listed in Table I is exemplified by the preparation of the following compound.

2-(2,6-Dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane Hydrochloride (10).—2-Aminomethyl-1,4-benzodioxane (17 g) and 2,6-dimethoxyphenoxyethyl chloride (10.8 g) were heated in an oil bath at 160° for 2 hr. After cooling, $CHCl_3$ (30 ml) and 2 *N* NaOH solution (50 ml) were added. The $CHCl_3$ layer was removed and the aqueous layer was extracted with $CHCl_3$ (two 10-ml portions). The combined $CHCl_3$ extracts were dried (Na_2SO_4) followed by filtration and distillation. A yellow viscous oil (10 g) of bp 234–238° (1 mm) was obtained. This oil was dissolved in *i*-PrOH (25 ml) and 4 *N* *i*-PrOH–HCl was added to slight acidity (7.2 ml). After standing for 3 days in a refrigerator, the solid was filtered and washed twice with a minimum of precooled (−5°) *i*-PrOH. Vacuum drying gave a white solid (**10**) (5 g) which is described in Table I.

2-Phthalimidomethyl-1,4-benzodioxane.—Potassium phthalimide (185 g) and 2-chloromethyl-1,4-benzodioxane (184.5 g) in DMF (400 ml) were refluxed with stirring for 2 hr. After cooling and pouring into H_2O (2 l.) the solid was filtered off and washed successively [H_2O (600 ml), 2% w/v NaOH (600 ml), H_2O (600 ml)]. Vacuum drying gave the crude product (263 g) of mp 201–202°. A sample recrystallized from 2-ethoxyethanol had mp 206–207°. *Anal.* ($C_{17}H_{13}NO_4$) C, H, N.

2-Aminomethyl-1,4-benzodioxane.—To a stirred refluxing solution of 2-phthalimidomethyl-1,4-benzodioxane (263 g) in 2-ethoxyethanol (1550 ml) a solution of $N_2H_4 \cdot H_2O$ (100%, 49 ml) in 2-ethoxyethanol (160 ml) was added over 5 min. During the addition an exothermic reaction occurred and a white solid crystallized out. After stirring and refluxing for another 1 hr, enough concentrated HCl (76 ml) was added at gentle reflux to give a nontransient blue color to congo red indicator paper. The mixture was cooled with stirring and filtered, the solid being washed with EtOH (three 170-ml portions). After distillation of the solvents under reduced pressure, the residue was dissolved in H_2O (1300 ml), the solution was filtered, and 5 *N* NaOH solution (400 ml) was added. Et_2O extraction (250 ml, then two 100-ml portions) followed by drying (Na_2SO_4), filtration, and distillation gave the product as a colorless oil (122.2 g), bp 121–122° (2 mm). The boiling point of 2-aminomethyl-1,4-benzodioxane is reported as 82–83° (0.75 mm) and 127–137° (4 mm).[8]

2,6-Dimethoxyphenoxyethanol.—2,6-Dimethoxyphenol (30.8 g) ethylene carbonate (35.2 g), K_2CO_3 (27.6 g), and toluene (40 ml) were stirred and refluxed for 2 hr. H_2O (150 ml) was added and the mixture was stirred to solution. The toluene layer was separated and extracted with 1 *N* NaOH (300 ml) and the remaining two alkaline solutions were extracted sequentially with C_6H_6 (three 25-ml portions). The combined toluene and C_6H_6 solutions were dried (Na_2SO_4), filtered, then distilled to give the product (31.4 g) as a colorless oil, bp 138–146° (3 mm).

2,6-Dimethoxyphenoxyethyl Chloride.—$SOCl_2$ (25.4 ml) was run into a stirred mixture of 2,6-dimethoxyphenoxyethanol (70.2 g) and pyridine (28.8 ml) at such a rate that the temperature did not exceed 80° with ice cooling. When the exothermic reaction was over, the mixture was stirred in a boiling-water bath for 2 hr prior to cooling and pouring into 2 *N* HCl (230 ml) and extraction with $CHCl_3$ (50 ml, two 30-ml portions). After washing the combined extracts with H_2O (50 ml) the solution was dried (Na_2SO_4), followed by filtration and distillation. The product (67.9 g) was obtained as a colorless oil, bp 128–132° (2 mm).

2,6-Dimethoxyphenoxypropyl Chloride.—After treating Na (2.3 g) with Cellosolve (75 ml) 2,6-dimethoxyphenol (15.4 g)

(5) (a) D. F. Marsh and J. F. O'Leary, *Federation Proc.*, **12**, 348 (1953); (b) J. F. O'Leary, *ibid.*, **12**, 355 (1953).

(6) D. Misiti, F. De Marchi, V. Rosnati, and D. Bovet, *J. Med. Pharm. Chem.*, **5**, 1285 (1962).

(7) (a) W. W. Carlson, U. S. Patent 2,448,767 (1948); (b) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1279 (1943).

(8) (a) J. Koo, *J. Org. Chem.*, **26**, 339 (1961); (b) G. B. Marrini-Bertolo, R. Landi-Vittory, and D. Bovet, *Gazz. Chim. Ital.*, **83**, 148 (1953).

TABLE II

ADRENOLYTIC AND CNS DEPRESSANT EFFECTS OF DERIVATIVES OF 1,4-BENZODIOXANE IN MICE

No.	n	R	Protection against epinephrine toxicity, ED_{50}, mg/kg *po*	Dose depressing CNS, mg/kg sc
1	2	CH_3	70	125
2	2	$CH_3OCH_2CH_2$	>100	50
3	2	$CH_3(OCH_2CH_2)_2$	>100	50
4	2	C_6H_5	15	500
5	2	*o*-$CH_3C_6H_4$	20	>1000[a]
6	2	2,6-$(CH_3)_2C_6H_3$	10	1000[a]
7	2	*o*-$CH_3OC_6H_4$	4	200
8	2	*m*-$CH_3OC_6H_4$	6	1000[a]
9	2	*p*-$CH_3OC_6H_4$	35	1000[a]
10	2	2,6-$(CH_3O)_2C_6H_3$	0.3	250
11	2	$C_6H_5CH_2$	>100	50
12	3	$CH_3OCH_2CH_2$	>100	25
13	3	C_6H_5	10	250
14	3	2,6-$(CH_3O)C_6H_3$	1.5	125
15	3	$C_6H_5CH_2$	100	50
16	4	C_6H_5	7	250
17	4	C_6H_5	>100	100[a,b]

[a] Toxic. [b] Convulsions.

was added followed by 3-bromopropyl chloride (19 g). The mixture was stirred under reflux for 2.75 hr, cooled, and filtered. Distillation gave the product (14.5 g) as a pale yellow oil, bp 130–140° (1 mm).

4,7-Dioxaoctyl Chloride.—3-Bromopropyl chloride (37.8 g) was added to a solution of sodium 2-methoxyethoxide (19.6 g) in 2-methoxyethanol (30.4 g) with stirring at 40°. After maintaining the temperature between 40 and 60° by intermittent cooling the mixture was heated on a steam bath for 1 hr. Inorganic matter was filtered from the cooled reaction mixture and the solid was washed (Et_2O). The combined filtrates were distilled through a short column packed with glass helices giving the product (5.7 g) as a colorless oil bp 184–196° (755 mm).

Pharmacological Methods. Protection against epinephrine toxicity was assessed by determining the dose of each compound required to protect mice against the lethal effect of epinephrine. Different doses of the test compounds were administered orally to groups of five male albino mice of 20–25 g. After 1 hr the mice were injected intraperitoneally with 20 mg/kg of epinephrine hydrochloride a dose which was found to kill 80% of the control group. The surviving mice were kept under observation for 5 days and the ED_{50} values were determined graphically.

Inhibition of the Pressor Effect in the Rat of Epinephrine and Norepinephrine.—Selected compounds were tested for their capacity to block the rise in blood pressure following the intravenous injection of epinephrine and norepinephrine in the anesthetized rat. Blood pressure was measured from the carotid artery by means of a mercury Condon manometer and recorded on a kymograph. Drugs were administered through a cannula in the jugular vein.

Action on the CNS.—Male albino mice (20–25 g) in groups of five were injected subcutaneously with the compounds at doses which ranged from ineffective to toxic doses. The animals were then observed for depression of spontaneous movement, loss of muscle tone, and head drop.

Results and Discussion

Pharmacology.—The epinephrine-protection test was found to be a useful screening procedure for selecting potential adrenolytic compounds. However, it has been reported that oral doses of 50 mg/kg of 2-diethylaminomethyl-1,4-benzodioxane (prosympal) and 2-piperidinomethyl-1,4-benzodioxane (piperoxan) failed to reduce the toxicity of epinephrine in mice.[9]

The compounds tested for adrenolytic activity by the mouse protection test and for their effect on the CNS are listed in Table II. Those compounds possessing adrenolytic activity had little or no effect on the nervous system at nontoxic doses. Compounds **2**, **3**, **11**, **12**, and **15** depressed the CNS without toxic side effects at the doses studied. It is of interest to note that with the exception of **15** none of these compounds showed adrenolytic properties in the mouse protection test at doses up to 100 mg/kg.

TABLE III

ANTAGONISM OF THE PRESSOR EFFECT OF EPINEPHRINE AND NOREPINEPHRINE ON THE RAT BLOOD PRESSURE

No.	Dose, mg/kg *po*	Mean % redn (range) of the pressor response induced by— Epinephrine (2–4 μg)	Norepinephrine (2–4 μg)
6	20	61 (47–77)	48 (31–81)
7	10	84 (79–92)	54 (38–70)
8	20	25 (10–40)	15 (10–20)
10	2.5	96 (92–100)	90 (80–100)
13	10	45 (43–47)	45 (41–49)
14	20	68 (36–76)	40 (27–55)
16	10	53 (42–70)	27 (20–41)

The subcutaneous injection of 25 mg/kg of **17** into mice resulted in hyperactivity, convulsions, and death at 50–100 mg/kg. This was an unusual effect as the related compounds **3** and **15** depressed the nervous system.

Meldrum and Bhargava[10] studied the effect of **17** on the EEG of the conscious rabbit and found that 5 mg/kg iv gave motor and electrocortical seizures. The injection of 10 mg/kg provoked clonic and tonic convulsions which terminated in death of the animal.

Compounds **6**, **7**, **10**, **13**, and **14** which were effective against epinephrine toxicity in doses of not more than 10 mg/kg were further investigated for epinephrine blockade in the anesthetized rat.

Table III shows that all the compounds tested were able to antagonize the pressor effect of epinephrine and norepinephrine. The most potent members of the series were **10** and **7**. A preliminary note on the pharmacology of these two compounds has been published.[11]

Structure–Activity Relationships.—It can be seen from Table II that the pharmacological properties of the series are dependent on the nature of R and the number of CH_2 groups attached to the terminal group.

Compounds in which R is alkoxy and $n = 2$ (**1**–**3**) or **12** in which $n = 3$, were characterized by their depressant effect on the CNS at nontoxic doses. The effect on the CNS remained unaltered if the alkoxy group was replaced by benzyloxy as in analogs **11** in which $n = 2$ and **15** in which $n = 3$; if $n = 4$ as in **17** the compound behaved as a convulsant. The evidence suggests that the convulsant or depressant properties may be determined by the number of methylene groups and the nature of the terminal group R.

Substitution of alkoxy or benzyloxy by a phenoxy terminal group gave compounds possessing adrenolytic properties (Table II). The unsubstituted phenoxy

(9) E. R. Loew and C. Micetich, *J. Pharmacol. Exptl. Therap.*, **93**, 434 (1948).

(10) B. S. Meldrum and V. K. Bhargava, *Intern. J. Neuropharmacol.*, **7**, 253 (1968).

(11) H. Fenton, P. N. Green, M. Shapero, and C. Wilson, *Nature*, **206**, 725 (1965).

analog **4** (n = 2) was less potent than **13** (n = 3) and **16** (n = 4) in protecting mice against the lethal effect of epinephrine.

Monosubstitution in the *ortho* position of the terminal phenoxy nucleus with CH_3 (**5**) did not result in increased potency. Compounds in which the CH_3 was replaced by *o*-CH_3O (**7**) and *m*-CH_3O (**8**) were more effective in the mouse protection test, but **8** was less potent in antagonizing the pressor response of epinephrine and norepinephrine in the anesthetized rat than **7** (Table III). The least active of the monosubstituted phenoxy series was **9** with *p*-CH_3O. In all these compounds n = 2.

Disubstitution with *o*-CH_3 (**6**) or *o*-CH_3O (**10**, **14**) gave compounds of increased potency. In the mouse protection test the 2,6-dimethoxy derivative (**10**, n = 2) was 30 times more potent than the corresponding dimethyl analog **6** (n = 2) and five times more potent than the 2,6-dimethoxy compound **14** (n = 3).

As a result of this preliminary investigation the hypotensive compound **10** [2-(2,6-dimethoxyphenoxy)ethylaminomethyl-1,4-benzodioxane] and the CNS depressant **2** [2-(3,6-dioxaheptyl)aminomethyl-1,4-benzodioxane] were selected for further study and the results will be published later.

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The Synthesis of 3,11β,17α-Trihydroxy-19-norpregna-1,3,5(10)-trien-20-one

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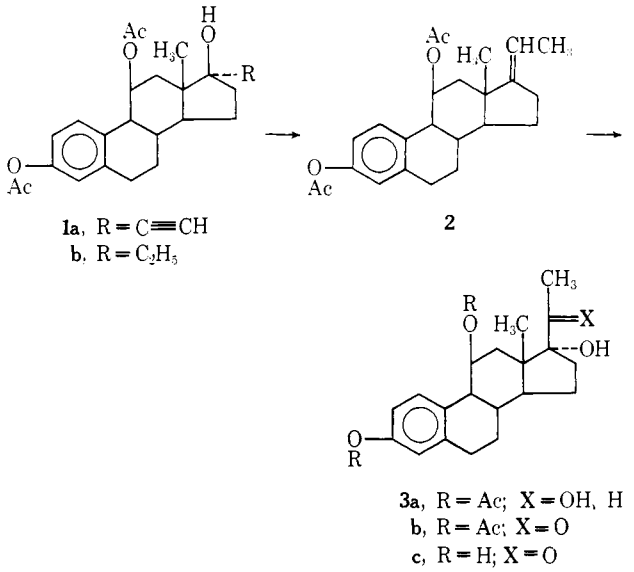
In order to examine the hormonal properties of some 3,20-bisoxygenated 19-norpregna-1,3,5(10)-trienes, the synthesis of 3,11β,17α-trihydroxy-19-norpregna-1,3,5-(10)-trien-20-one (**3c**) was undertaken. This substance, previously available only by microbiological fermentation,[1] was prepared in a synthesis beginning with the diacetate **1a**, obtained by hydrogenation of the readily available 11β-hydroxy-17α-ethynylestradiol.[2] The hydrogenated product **1b** was dehydrated with $SOCl_2$ and pyridine to **2** and then oxidized with OsO_4 in pyridine[3] to the diol **3a** (Scheme I). Oxidation of the diol **3a** with CrO_3 in the presence of $MnCl_2$[4] gave the ketone **3b** which was hydrolyzed to **3c**. The ORD curve of **3c**, which exhibits a positive Cotton effect, establishes the 17β configuration of the acetyl group.

Biology.—The pregnatriene **3c** exhibited antiinflammatory activity in the cotton granuloma assay[5] at 25 mg when administered by injection and no activity at 5 mg when administered orally. When tested for its estrogenic activity by injection using estrone as a standard in the mouse uterine-growth assay,[6] it was active at 0.1 mg and, when tested for antiandrogenic activity[7] at 5 mg by injection, the substance exhibited no activity.

SCHEME I



Experimental Section[8]

3,11β-Diacetoxy-17α-ethynylestra-1,3,5(10)-trien-17β-ol (1a).—When 2.2 g of 11β-hydroxyethynylestradiol[2] was acylated with Ac_2O and pyridine for 24 hr at 25°, 2.0 g of crude **1a** was obtained. Crystallization of the crude product from Et_2O gave an analytical sample, mp 160–163°, $[\alpha]^{25}D$ −9° ($CHCl_3$). *Anal.* ($C_{24}H_{28}O_5$) C, H.

3,11β-Diacetoxy-17α-ethylestra-1,3,5(10)-trien-17β-ol (1b).—When 15.5 g of **1a** was hydrogenated in 250 ml of EtOAc in the presence 1.5 g of 5% Pd–C at atmospheric pressure, 16 g of crude **1b** was obtained. Crystallization of the crude product (Me_2CO) and hexane gave an analytical sample, mp 195–196°, $[\alpha]D$ +53.5° ($CHCl_3$). *Anal.* ($C_{24}H_{32}O_5$) C, H.

3,11β-Diacetoxy-19-norpregna-1,3,5(10),17(20)-tetraene (2).—A solution of 15.3 g of **1b** in 120 ml of pyridine was added dropwise, with stirring over 30 min, to a solution of 8.6 g of $SOCl_2$ in 75 ml of pyridine maintained at −15°. The solution was allowed to come to 20°, then cooled to 0°, diluted with 5 ml of EtOH and 2.2 l. of $CHCl_3$, and stirred. The $CHCl_3$ solution was washed with three 300-ml portions of H_2O and 300 ml of aqueous $NaHCO_3$, dried ($MgSO_4$), and distilled to dryness. Since some hydrolysis at the C-3 acetate occurred, the crude product was dissolved in 30 ml of pyridine and 15 ml of Ac_2O. After 30 min ice and H_2O were added to the solution. Trituration at 0° yielded a crystalline material which was collected by filtration. The crude product, mp 118–123°, weighed 12.3 g. Crystallization of the crude product from CH_2Cl_2 and MeOH gave an analytical sample: mp 147–150°; nmr maxima at 54 (C-13 methyl), 89 and 96 (C-20 methyl), and 303 (multiplet, C-20 H) cps; $[\alpha]^{25}D$ +54° ($CHCl_3$). *Anal.* ($C_{24}H_{30}O_4$) C, H.

3,11β-Diacetoxy-17α-hydroxy-19-norpregna-1,3,5(10)-trien-20-one.—A solution of 12.6 g of crude **2** in 75 ml of pyridine was mixed with a solution of 8.4 g of OsO_4 in 50 ml of pyridine and allowed to stand for 18 hr. To the solution was then added with

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