Adrenal Cortical Inhibitors and Potent Synthetic Estrogens

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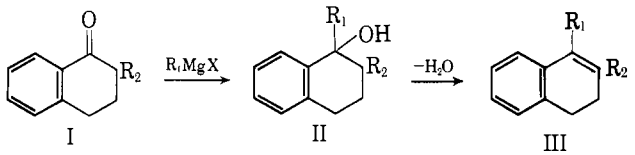
A number of substituted 1,2-diaryldihydronaphthalenes have been prepared. Substances containing the 3-pyridyl moiety partially inhibited biosynthesis of corticosteroids in the dog. A few of the described compounds were found to be potent estrogens. Their potency was compared with the natural hormone estradiol.

In the course of our continued search for adrenal cortical inhibitors we have prepared and tested a large number of compounds which contained the 3-pyridyl moiety. Among these substances several pinacolone-type ketones were found to inhibit preferentially the 11β-hydroxylase enzyme system.[1,2] One of these inhibitors, metyrapone,[3] is in clinical use as a diagnostic agent for the determination of pituitary reserve.

Another series of compounds with 3-pyridyl groups which have been prepared are the tetralones (I) and dihydronaphthalenes (III). Substances I (R_2 = 3-pyridyl) and III (R_1 = H or CH_3; R_2 = 3-pyridyl) proved to be preferential inhibitors of the 17α-hydroxylase enzyme systems in the adrenal cortex.[4,5]



I II III

Compound I (R_2 = 3-pyridyl) was reported to reduce secretion of aldosterone by 80 to 90% in men.[6]

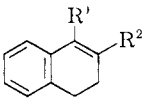
(R_2 = 3-pyridyl,[4] phenyl,[7] *p*-methoxyphenyl[8]) with Grignard reagents. The free phenolic substances were obtained by demethylation of the corresponding methoxy compounds.

In the case of preparation of **1** the hydrated intermediate (II) has been isolated, whereas dehydration occurred spontaneously in the synthesis of **3**, **5**, and **7**.

The Grignard reactions leading to the desired dihydronaphthalenes were carried out in the usual manner and offered no difficulties. However, demethylation of the anisole derivatives presented some problems worthy of note. When demethylation of **3** was carried out in a boiling mixture of acetic acid and hydrobromic acid, considerable amounts of 2-phenylnaphthalene were isolated. The strong acidic medium at elevated temperature elicited an unusual disproportionation, the first step of which may have been a reversed Friedel–Crafts reaction. Elimination of substituent R_1 by protonation occurred concurrently with dehydrogenation of the dihydronaphthyl residue to 2-phenylnaphthalene. Application of the less acidic pyridine hydrochloride as an O-demethylating agent was more rewarding and afforded the desired dihydronaphthalenes **2**, **4**, **6**, and **8** in moderate yields.

TABLE I

1,2-DIARYL-3,4-DIHYDRONAPHTHALENES



Compd.	R_1	R_2	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	4-$CH_3OC_6H_4$	3-C_5H_4N	21	130–131	$C_{22}H_{19}NO$	84.31	6.11	4.48	84.32	5.90	4.40
2	4-OHC_6H_4	3-C_5H_4N	81	296–298	$C_{21}H_{17}NO$	84.25	5.72	4.68	84.37	5.78	4.63
3	4-$CH_3OC_6H_4$	C_6H_5	84	131–132	$C_{23}H_{20}O$	88.42	6.45		88.67	6.29	
4	4-OHC_6H_4	C_6H_5	63	128–130	$C_{22}H_{18}O$	88.56	6.08		88.36	6.01	
5	C_6H_5	4-$CH_3OC_6H_4$	56	149–150	$C_{23}H_{20}O$	88.42	6.45		88.17	6.44	
6	C_6H_5	4-OHC_6H_4	52	154–155	$C_{22}H_{18}O$	88.56	6.08		88.66	5.96	
7	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	62	168–169	$C_{24}H_{22}O_2$	84.17	6.47		88.35	6.46	
8	4-OHC_6H_4	4-OHC_6H_4	43	258–260	$C_{22}H_{18}O_2$	84.05	5.77		84.34	5.61	

The chemistry and hormonal or antihormonal activity of eight compounds of the type III, where both R_1 and R_2 are aryl groups, serve as the subject matter of this report.

Chemistry.—The compounds listed in Table I were prepared by treating the appropriate tetralones I

The structures assigned to compounds **1**–**8** are in agreement with their infrared and ultraviolet spectra. As additional structural proof, **4** was remethylated under mild conditions. The methylated product was found to be identical with **3**. Thus, no migration of substituents or shift of double bond occurred during demethylation with pyridine hydrochloride.

Pharmacology. Steroid Biosynthesis.—Inhibition of corticosteroid hormones *in vivo* was assessed in the dog by the adrenal cannulation technique. Compound **1**

(1) W. L. Bencze and M. J. Allen, *J. Med. Pharm. Chem.*, **1**, 395 (1959).
(2) J. J. Chart and H. Sheppard, *ibid.*, **1**, 407 (1959).
(3) Metopirone®.
(4) W. L. Bencze and L. I. Barsky, *J. Med. Pharm. Chem.*, **5**, 1298 (1962).
(5) J. J. Chart, H. Sheppard, T. Mowles, and N. Howie, *Endocrinology*, **71**, 479 (1962); *Chem. Abstr.*, **57**, 17303 (1962).
(6) T. Bledsoe, D. P. Island, A. Riondel, and G. W. Liddle, *Clin. Res.*, **11**, 214 (1963).
(7) N. Campbell and D. Kidd, *J. Chem. Soc.*, 2154 (1954).
(8) M. S. Hidayetulla, R. C. Shah, and T. S. Wheeler, *ibid.*, 111 (1941).

decreased cortisol secretion to 10% of controls and increased corticosterone secretion to 300% of control values during a 2-hr. period following the administration of a 20-mg./kg. dose intravenously. No increase in secretion of Reichstein's compound S was observed. This change in corticosteroid secretion pattern is similar to that observed following administration of substance I (R_2 = 3-pyridyl) and, therefore, the compound could be classified as a preferential inhibitor of 17α-hydroxylation as discussed by Chart, *et al.*[5] Compound **2** was not tested in the dog because its low solubility precluded intravenous administration.

Uterotropic Activity.—The eight compounds shown in Table I were suspended in a vehicle containing carboxymethylcellulose and given by subcutaneous injection for 3 days to immature female rats of the CIBA strain weighing 40–50 g. On the fourth day the animals were sacrificed, and the uteri were removed, expressed of fluid, cleaned of adhering tissue, and immediately weighed on a Roller–Smith balance. The results, as seen in Table II, indicate the amount of test compound required to produce uterine stimulation equivalent to that produced by subcutaneous administration of 2.0 γ/kg. of estradiol for 3 days.

TABLE II

UTEROTROPHIC ACTIVITY OF 1,2-DIARYL-3,4-DIHYDRONAPHTHALENES

Compd.	Dose, γ/kg.[a]
1	25,000
2	25,000
3	200.00
4	20.0
5	32.0
6	20.0
7	100.0
8	25.0

[a] Dose that produces the same activity as 2.0 γ/kg. of estradiol.

Antiestrogenic Activity.—No antiestrogenic response was elicited when any of the eight compounds, in a variant dose range of 250 γ/kg. to 50 mg./kg., were given concomitantly with estradiol to immature female rats for 3 days. Basic phenolic ethers derived from **4** were found to possess antiestrogenic activity only when marked uterotropic stimulation with larger doses of estradiol (10 γ/kg.) was attained in immature female rats. Duncan, *et al.*, also reported antiestrogenic activity of basic ethers of **4** when administered to ovariectomized rats.[9]

Experimental[10]

3,4-Dihydro-1-*p*-methoxyphenyl-2-(3-pyridyl)naphthalene (1).—To a Grignard reagent prepared from 2.4 g. (0.1 g.-atom) of magnesium and 18.7 g. (0.1 mole) of *p*-methoxybromobenzene in 100 ml. of ether was added dropwise with cooling and stirring 15.0 g. (0.067 mole) of 3,4-dihydro-2-(3-pyridyl)-1(2H)-naphthalenone.[4] After completed addition the reaction mixture was heated under reflux for 4 hr. and allowed to stand at room temperature overnight. Upon decomposition with aqueous ammonium chloride solution, a crystalline precipitate formed which was collected, washed with water, and recrystallized from ethanol to afford the intermediate II (R_1 = *p*-methoxyphenyl; R_2 = 3-pyridyl), m.p. 190–195°, 6.2 g.

This intermediate product (5.0 g.) was dissolved in a mixture of 100 ml. of ethanol and 60 ml. of concentrated HCl and refluxed for 1 hr. After removal of the ethanol under reduced pressure, the acidic solution was neutralized with concentrated ammonium hydroxide and the precipitate was extracted three times with ethyl acetate. The combined extracts were washed with water and saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to dryness *in vacuo* to afford 3.4 g. of the crude product. After recrystallization from ethanol and water the pure product melted at 130–131°.

Compounds **3**, **5**, and **7** have been isolated directly after decomposition of the corresponding Grignard complexes.

3,4-Dihydro-1-*p*-hydroxyphenyl-3-(3-pyridyl)naphthalene (2).—Anhydrous pyridine hydrochloride was prepared by gradually heating a mixture of 30 ml. of pyridine and 38 ml. of concentrated HCl until crystalline pyridine hydrochloride appeared in the condenser. At this point, the temperature of the vapor phase was 216° and that of the bath 260°. Heating was now discontinued and when the temperature of the liquid pyridine hydrochloride dropped to approximately 150°, 2.8 g. of **1** was dissolved in it by swirling the flask. Heating was resumed and the reaction mixture was gently refluxed for 30 min. The temperature of the bath was kept between 245 and 255°. No demethylation occurred below 230°. The reaction mixture was allowed to cool to about 100–150°, poured into ice water, and buffered with 20 g. of sodium acetate. The precipitated crude product was collected and air dried, m.p. 290–296°. Recrystallization from a mixture of dimethylformamide, ethanol, and water (1:1:1) furnished 2.15 g. of **2**, m.p. 294–296°. A sample was sublimed for analysis.

Compound **4** was prepared repeatedly by demethylation of **3** in pyridine hydrochloride. In contrast to the phenolic compounds **2**, **6**, and **8**, purification of phenol **4** required several crystallizations. Nevertheless, specimens of **4** melting in the temperature range of 120–126° were found to be sufficiently pure by analyses and they furnished various O-alkylated derivatives in good yield, which, in turn, could be easily purified.

In one instance 2-phenylnaphthalene was isolated as a minor contaminant of **4** when **3** was demethylated in pyridine hydrochloride at 260° (bath temperature).

Phenol **6** has been isolated in two crystalline forms, m.p. 130–133° and m.p. 154–155°. A mixture of these two forms melted undepressed at the higher melting point, 154–155°.

2-Phenylnaphthalene.—Compound **3** (2.0 g.) was refluxed in a mixture of 50 ml. of glacial acetic acid and 50 ml. of 48% HBr for 6 hr. The reaction mixture was poured into ice water, and the crystalline precipitate was collected. Recrystallization from ethanol gave 0.65 g. of a colorless product, m.p. 101–102°. A second crop 0.30 g., m.p. 82–90°, was isolated from the filtrate. This product was identified as 2-phenylnaphthalene by analysis, spectral data, and undepressed mixture melting point with an authentic specimen prepared according to the method of Campbell.[7] No attempt was made to isolate **4**.

Remethylation of 4 to 3.—Substance **4** (2.0 g.) was converted to its sodium salt in 10 ml. of dimethylformamide by addition of 320 mg. of sodium hydride (53% mineral oil suspension). After the cessation of hydrogen evolution 1.05 g. of methyl iodide in 10 ml. of toluene was added with stirring and cooling in an ice bath. Stirring was continued for 4 hr. at room temperature and the reaction mixture was allowed to stand at room temperature for 18 hr. The sodium iodide–dimethylformamide complex was collected and washed with benzene. The filtrate was concentrated to 3–4 ml. *in vacuo* and diluted with water. The precipitated colorless product was collected and recrystallized from ethanol to afford 1.5 g. of **3**, m.p. 130–132°. A sample was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{29}H_{29}O$: C, 88.42; H, 6.45. Found: C, 88.50; H, 6.47.

This product was found to be identical with **3**, as prepared from 2-phenyltetralone and *p*-methoxyphenylmagnesium bromide, by mixture melting point and superimposable infrared absorption spectra.

(9) G. W. Duncan, S. C. Lyster, J. J. Clark, and D. Lednicer, *Proc. Soc. Exptl. Biol. Med.*, **112**, 439 (1963).

(10) Melting points were determined in an electrically heated aluminum block.