Basic Ethers of 1-(*p*-Hydroxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinoline and 1-(*p*-Hydroxyphenyl)-2-phenylindole. Antifertility Agents

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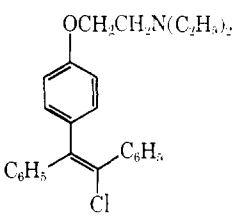
The diethylaminoethyl and pyrrolidinylethyl ethers of 1-(*p*-hydroxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinoline (**8**, R′ = H), 1-(*p*-hydroxyphenyl)-2-phenylindole (**25**), and 1-(*p*-hydroxyphenyl)-5-methoxy-2-phenylindole (**26**) were synthesized as potential antifertility agents. The intermediate tetrahydroquinoline **8** (R′ = CH_3) was prepared by three different routes, the key steps of which were, respectively, acid-catalyzed cyclization of 3-[*o*-(*p*-anisidino)phenyl]-1-phenyl-1-propanol (**7**), LAH–$AlCl_3$ reduction of 1-(*p*-methoxyphenyl)-2-phenyl-4-(1*H*)-quinolone (**14**), and KNH_2-induced cyclization of *N*-[3-(2-chlorophenyl)-1-phenylpropyl]-*p*-anisidine (**20**). The intermediate indoles **25** and **26** have been synthesized by dehydrogenation of the corresponding 4,5,6,7-tetrahydroindoles available from the condensation of 2-(2-oxocyclohexyl)- and 2-(2-oxo-5-methoxycyclohexyl)acetophenone (**21** and **22**) with *p*-aminophenol. The basic ethers exhibited antifertility, estrogenic, and antiestrogenic activity in the female rat.

Reports of the antifertility properties of triarylethylene derivatives such as **1**[1] and **2**[2] have stimulated the synthesis and evaluation of a number of closely related substances.[3]



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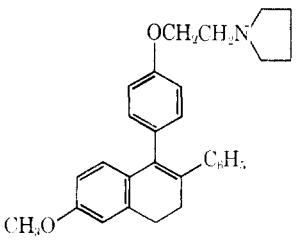

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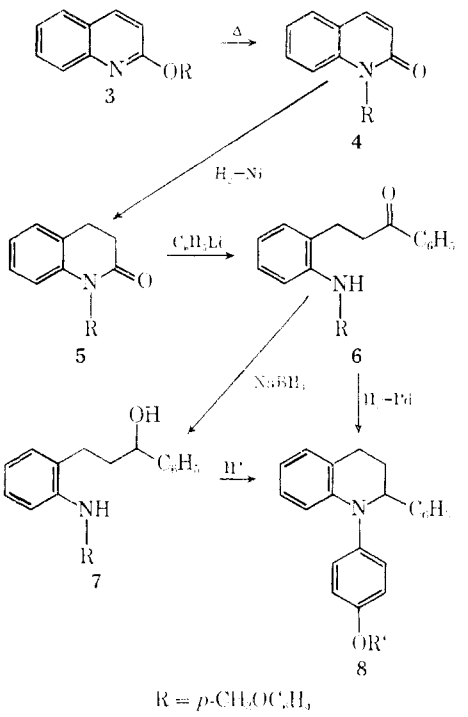
The subject of this report is the synthesis of related 1,2-diaryltetrahydroquinolines and 1,2-diarylindoles (Table I) and our assessment of their antifertility, estrogenic, and antiestrogenic activities in the rat.

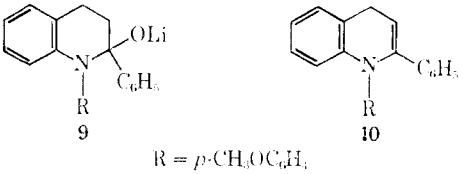
We have developed three synthetic routes (Schemes I–III), which proved to be of varying utility, for the preparation of the intermediate tetrahydroquinoline **8** (R′ = CH_3). A notable conversion in Scheme I is the reaction of excess PhLi and the dihydrocarbostyril **5** from which the open-chain ketone **6** was obtained in 82% yield. It is possible that the product remains in the ring-closed form **9** prior to hydrolysis, yet, attempts to convert the ketone **6** into the cyclic enamine **10** were unsuccessful, and there was no spectral evidence for the existence of an appreciable portion of the ketone in the cyclic carbinolamine form. Catalytic hydrogenation, nevertheless, afforded the ring-closed product **8** (54%) accompanied by the alcohol **7** (30%). The alcohol did not undergo ring closure under these conditions. The more convenient procedure for the preparation of large amounts of **8** (R′ = CH_3) was found to be reduction of **6** with $NaBH_4$ followed by cyclization of alcohol **7** in

Scheme I



R = *p*-$CH_3OC_6H_4$

boiling xylene in the presence of *p*-toluenesulfonic acid. The reduction was quantitative and the cyclization proceeded in 94% yield when the initial concentration of



R = *p*-$CH_3OC_6H_4$

7 in the reaction mixture was 2.6 wt/vol %. An increase in the concentration of **7** to 5.6% decreased the yield of **8** to 34%, probably a result of competion from intermolecular side reactions.

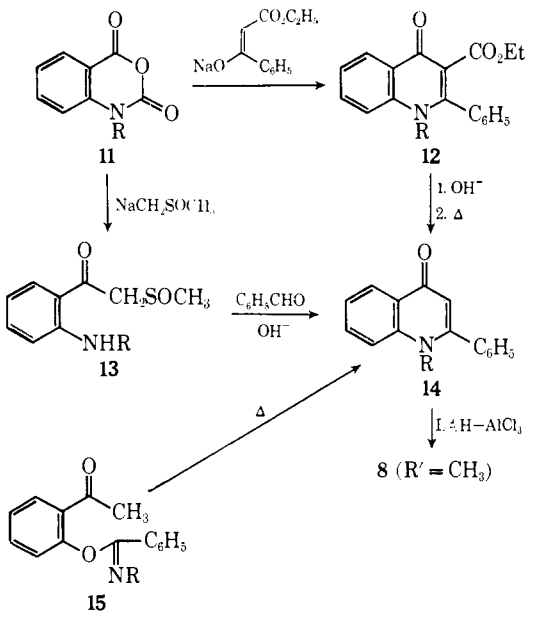
A second initially attractive pathway to **8** (R′ = CH_3) featured reduction of the corresponding quinolone **14**. Three useful routes to this intermediate are shown in Scheme II.

(1) D. E. Hollkamp, J. G. Greslin, C. A. Root, and L. J. Lerner, *Proc. Soc. Exp. Biol. Med.*, **105**, 197 (1960).

(2) G. W. Duncan, S. C. Lyster, J. J. Clark, and D. Ledniicer, *ibid.*, **112**, 439 (1963).

(3) (a) A lead reference: R. W. J. Carney, W. L. Beneze, J. Wojcikunski, A. A. Renzi, L. Dorfman, and G. deStevens, *J. Med. Chem.*, **9**, 516 (1966); (b) J. K. Landquist and C. J. Marsden, *Chem. Ind. (London)*, 1032 (1958); H. A. DeWald, O. D. Bird, G. Rodney, D. H. Kaump, and M. L. Black, *Nature (London)*, **211**, 538 (1966); (d) M. J. K. Harper and A. L. Walpole, *J. Endocrinol.*, **37**, 83 (1967).

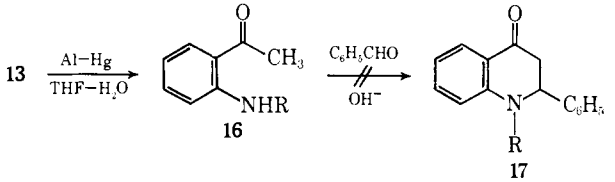
SCHEME II



R = p-$CH_3OC_6H_4$

The quinolone lacking MeO has been prepared by Chapman by pyrolysis of the imino ether corresponding to **15**.[4] The conversion of **11** into **12** has precedent,[5] and the condensation of the β-keto sulfoxide **13** with PhCHO to give **14** finds analogy in Taylor's new quinolone synthesis.[6] The difficulty in Scheme II lies in the reduction of the very stable pyridone ring system of **14**. The compound was either unaffected or converted into intractable mixtures after exposure to a variety of reduction environments. Only by reduction with LAH–$AlCl_3$ in THF was it possible to generate an appreciable amount of the tetrahydroquinoline **8** (R′ = CH_3) and then in only 35% yield.

In an effort to prepare the dihydroquinolone **17,** the readily available Me ketone **16** was condensed with PhCHO in the presence of alkali. The product, which appeared to be a single compound on the basis of melting point, tlc, and analytical criteria, nevertheless exhibited complex ir and nmr spectra indicative of a mixture of open-chain benzylidene derivatives.[7] Attempts

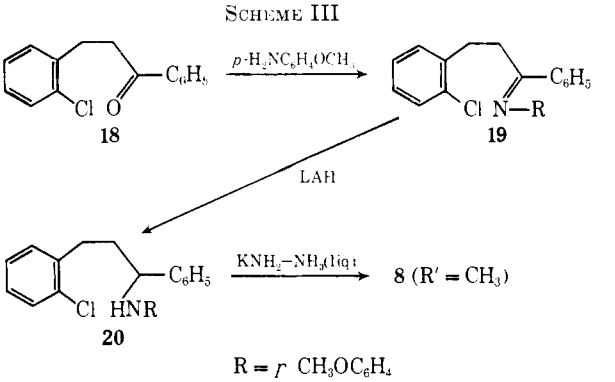


R = p-$CH_3OC_6H_4$

to effect cyclization to **17** were fruitless. Treatment of the PhCHO condensation product with LAH–$AlCl_3$ in THF gave only a small amount of **8**.

A third synthesis of **8** (R′ = CH_3) is outlined in Scheme III. Here the important step is the KNH_2-induced cyclization of **20,** a process which undoubtedly proceeds through a benzyne intermediate.[8] The method is an extension of Bunnett's general scheme for preparation of heterocycles *via* benzynes.[9] Demethylation of **8** (R′ = CH_3) and alkylation of the resulting phenol **8** (R′ = H) gave the required basic ethers (Table I).

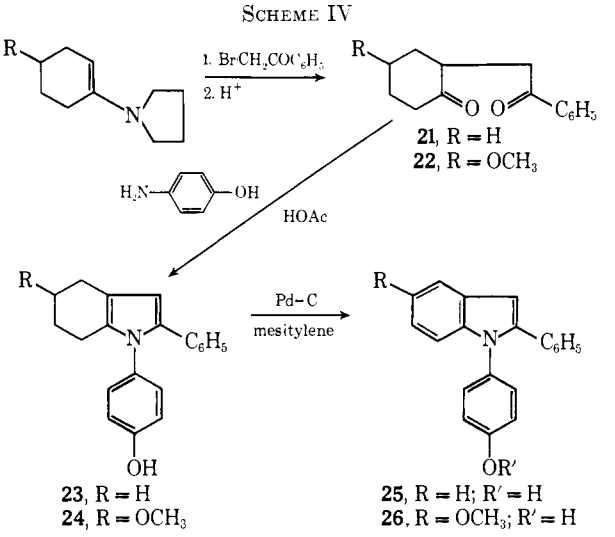
SCHEME III



R = *p* $CH_3OC_6H_4$

The 1,2-disubstituted indoles **25** and **26** were synthesized in two simple steps from the readily available cyclohexanone derivatives **21** and **22** as outlined in Scheme IV.

SCHEME IV



Of more than passing interest is the dehydrogenation of **24** to **26,** a process in which the MeO group is retained. The yield of dehydrogenation product was 78%. This result is not without precedent since, in a study of the dehydrogenation of hydroaromatic alcohols, Linstead[10] reported that *ac*-β-tetralol is dehydrogenated to β-naphthol in 60% yield. It should also be noted that dehydrogenation of substituted 4,5,6,7-tetrahydroindoles has received little attention as a synthetic route to substituted indoles and could prove to be a useful complement to classical methods. The basic ethers which were prepared from **25** and **26** are listed in Table I.

Biological Activity.—The dose of each compound which produced a minimal but significant increase in

(4) A. W. Chapman, *J. Chem. Soc.*, 1743 (1927).
(5) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).
(6) A. M. van Leusen and E. C. Taylor, *ibid.*, **33**, 66 (1968).
(7) Th. Kappe and E. Ziegler, *Monatsh. Chem.*, **94**, 935 (1963), assigned the chalcone structure to the product of condensation of 2′-anilinoacetophenone and benzaldehyde.
(8) This route was suggested to us by Professor Ronald Breslow.
(9) J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963).
(10) R. P. Linstead and K. O. A. Michaeles, *J. Chem. Soc.*, 1134 (1940).

the weight of the uterus of immature female rats is shown in Table I. It was observed that a tenfold increase in the dose of these compounds did not produce any further increase in the weight of the uterus. This type of dose–response relationship suggests that these compounds are impeded estrogens.[11] It can be seen from Table I that, with the exception of **2**, the dose of each compound which produced a minimal but significant increase in the weight of the uterus also significantly inhibited the uterotrophic response to estradiol as well as completely prevented pregnancy.

Table I

Oral Estrogenic, Antiestrogenic, and Antifertility Activities in the Rat

	Compound	Estrogenic,[a] mg/kg per day × 3	Anti-estrogenic,[b] mg/kg per day × 3	Anti-fertility,[c] mg/kg per day × 6
8,	R′ = $CH_2CH_2NEt_2$	100	100	100
8,	R′ = CH_2CH_2N⟨ ⟩	25	25	50
25,	R′ = $CH_2CH_2NEt_2$	10	12.5	25
25,	R′ = CH_2CH_2N⟨ ⟩	10	12.5	12.5
26,	R′ = $CH_2CH_2NEt_2$	2	10	2
2		0.01	1.0	0.05

[a] Dose which produced minimal but significant increase in the weight of the uterus. [b] Dose which significantly inhibited the uterotrophic responsiveness to 17β-estradiol (0.002 mg/kg per day × 3, sc). [c] Minimum dose which completely prevented pregnancy.

When a partially effective dose of **25** (R′ = $CH_2CH_2NEt_2$) was used, implantation occurred but fetal development was delayed. This result suggests that the compound inhibits the effects of the estrogen surge and delays implantation. Harper and Walpole[3d] have shown that estrone can cause implantation to occur after implantation had been delayed in the rat by *trans*-1-(*p*-β-dimethylamino ethoxyphenyl)-1,2-diphenylbut-1-ene. Staples[12] showed that clomiphene (**1**) also prevents implantation in the rat. Both the estrogenic and antiestrogenic activities of the present series of compounds appear to contribute to their effectiveness as antifertility agents in the rat.

The basic ethers listed in Table I are close structural relatives of a large number of experimental drugs[1–3] reported to have the same activity. All of these drugs appear to have varying degrees of estrogenic and antiestrogenic activity, and it seems clear from the data in Table I that the compounds reported here are not different in this respect. It should be noted that **1** and **2** are ineffective in blocking pregnancy in the monkey.[13] There have been no reports of the antifertility properties of these drugs in man.

Experimental Section

Melting points were taken in capillary tubes in an oil bath. They are not corrected but are within 1° of the melting points of standards. Spectra were determined under the supervision of Dr. R. K. Kullnig. Nmr spectra were determined with a Varian Model A-60 nmr spectrometer (TMS unless otherwise indicated). The nmr, uv, and ir spectra of most of the compounds were determined and are in accord with the structures written.

Analyses were carried out under the supervision of Mr. K. D. Fleischer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

2-(*p*-Methoxyphenoxy)quinoline (3).—The compound was prepared from 2-chloroquinoline and *p*-methoxyphenol by Scherrer's procedure,[14] mp 96.5–98° (C_6H_6–hexane). *Anal.* ($C_{16}H_{13}NO_2$) C, H, N.

1-(*p*-Methoxyphenyl)carbostyril (4).—The carbostyril was prepared in 50–65% yield by heating **3** in Nujol at 350–380° for 4 hr under N_2. It was recrystd from C_6H_6, mp 153–155° and 163–164°. *Anal.* ($C_{16}H_{13}NO_2$) C, H, N.

1-(*p*-Methoxyphenyl)-3,4-dihydrocarbostyril (5).—The reduction of **4** was carried out in abs EtOH in the presence of Raney Ni at 50–60° and H_2 at 39 kg/cm², 80% yield, mp 161.5–165° (*i*-PrOH). *Anal.* ($C_{16}H_{17}NO_2$) C, H, N.

3-[*o*-(*p*-Anisidino)phenyl]propiophenone (6).—A warm soln of 37.5 g (0.148 mol) of **5** in 280 ml of C_6H_6 was added in one portion to 405 ml of PhLi (0.222 mol in C_6H_6–Et_2O, 75:25 vol %, Foote Mineral Co.) and stirred at reflux for 2.5 hr under N_2. C_6H_6 (300 ml) and ice–H_2O (450 ml) were added at ice temp. The organic phase was sepd, washed (H_2O), dried (Na_2SO_4), and evapd to give 40 g (82%) of product, mp 110–113°. It was recrystd from C_6H_6–hexane: mp 110.5–112°; ir ($CHCl_3$) 2.98 (NH), 5.95 μ (C=O); nmr (20% DCCl₃) δ 6.15–8.1 (m, 14–15, aryl and NH), 3.73 (s, 3, OCH_3) and 3.16 ppm (A_2B_2, 4, C_2HCH_2). *Anal.* ($C_{22}H_{21}NO_2$) C, H, N.

3-[*o*-(*p*-Anisidino)phenyl]-1-phenyl-1-propanol (7). This compd was obtained in high yield from the reduction of **6** with LAH or $NaBH_4$: mp 90.5–92° (hexane). *Anal.* ($C_{22}H_{23}NO_2$) C, H, N.

1-(*p*-Methoxyphenyl-2-phenyl-1,2,3,4-tetrahydroquinoline (8, R′ = CH_3). A. By Hydrogenation of 6.—A soln of 1.67 g of **6** in 125 ml of EtOH was shaken with 0.50 g of 10% Pd–C and H_2 at 2.6 kg/cm². H_2 (1 mol-equiv) was absorbed at 60° in 40 min. The product was chromatographed on 100 g of Florisil. Elution with 1.5 l. of C_6H_6–hexane, 1:1, afforded 0.85 g (54%) of a colorless oil which consisted almost entirely (tlc) of **8**, (R′ = CH_3). It crystallized from hexane, mp 91.5–93.5°. *Anal.* ($C_{22}H_{21}NO$) C, H, N. Elution with C_6H_6–Et_2O, 20:1 gave 0.50 g (30%) of an oil whose ir spectrum was identical with that of **7**.

B. By Acid-Catalyzed Cyclization of 7.—A soln of 45 g (0.135 mol) of **7** and 5.0 g (0.026 mole) of *p*-toluenesulfonic acid monohydrate in 1700 ml of xylene was stirred at reflux for 5 hr under N_2. Et_2O was added to the cooled reaction mixture and the soln was washed (satd $NaHCO_3$). The dried (Na_2SO_4) filtrate was concd to give 40 g (94%) of **8**, (R′ = CH_3) as a brown oil which crystallized, mp 88–91°, identical (ir) with authentic **8**, (R′ = CH_3).

C. By Reduction of 14.—To 1 g (0.008 mol) of anhyd $AlCl_3$ and 2.5 g (0.066 mol) of LAH in 50 ml of THF was added 2.5 g (0.008 mol) of **14** in 70 ml of THF. The soln was stirred at room temp for 15 hr. The product was isolated in the usual manner to afford a gum which now exhibited strong ir absorption ($CHCl_3$) at 5.96 μ (**14**, C=O, 6.16 μ). After a second exposure to the identical reduction conditions the crude mixture was transparent in the 6-μ region. Chromatography as in A (*vide supra*) afforded 0.90 g (35%) of white crystals, mp 91–93°, undepressed on admixture with authentic **8**, (R′ = CH_3).

Initially it seemed reasonable to assume the 5.96-μ component of the first reduction mixture was the dihydroquinolone **17**. The enolate anion of this ketone could have formed by addition of hydride at C-2 and resisted further reduction. Glpc examination of the reduction products revealed, however, that the second exposure to reducing agent did not increase the yield of **8** (R′ = CH_3). Furthermore, tlc and ir studies showed that neither **6** nor the product(s) from the condensation of PhCHO with the Me ketone **16** could be responsible for the absorption at 5.96 μ. Thus the 5.96-μ product remains unidentified.

D. By Cyclization of 20.—Crude **20** (4.5 g, 80% pure by glpc, 0.0113 mol) was stirred for 3 hr in 250 ml of liq NH_3 containing KNH_2 from 4 g (0.104 g-atom) of K. The product, 4.4 g of a gum, contained 51% **8**, (R = CH_3 glpc analysis).

1-(*p*-Hydroxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinoline (8, R′ = H).—This phenol was obtained as a glass by HBr–HOAc

(11) C. Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 347 (1955).

(12) R. E. Staples, *Endocrinology*, **78**, 82 (1966).

(13) J. M. Morris, G. V. Wagenen, T. McCann, and D. Jacob, *Fed. Steril.*, **18**, 18 (1967).

(14) R. V. Scherrer, German Patent 1,186,870 (1965); *Chem. Abstr.*, **63**, 513 (1965).

cleavage of the Me ether **8** (R′ = CH_3). Alternatively the crude product from the cyclization of **20** with KNH_2 was demethylated by heating with KOH in ethylene glycol at 220° for 6 hr. Ethereal HCl converted the product into the unstable **hydrochloride**, mp 189–192° dec.[15] *Anal.* ($C_{21}H_{19}NO \cdot HCl$) C, H, N.

***N*-(*p*-Methoxyphenyl)isatoic Anhydride (11).**—*N*-(*p*-Methoxyphenyl) anthranilic acid[16] (51 g, 0.21 mol) and 210 ml of ethyl chloroformate were stirred at reflux for 17 hr. The mixture was concd and the product was collected and washed (Et_2O): yield 53 g (94%); mp 214–216°. It was recrystd from THF, mp 214–215°. *Anal.* ($C_{15}H_{11}NO_4$) C, H, N.

2-Methylsulfinyl-2′-(*p*-anisidino)acetophenone (13).—Dimsyl sodium[17] (365 ml of a 2 *M* soln) was stirred under N_2 at 10° while 65 g (0.24 mol) of the anhydride **11** in 150 ml of DMSO was added. The temp rose to 38° despite external cooling. After 0.5 hr at 25° and 1 hr at 50°, the soln was poured on ice and the mixture was acidified and extracted (CH_2Cl_2). Concn of the dried extracts left 69 g of residue. Two recrystallizations (C_6H_6–cyclohexane) gave 50 g (69%) of yellow crystals, mp 115–116°. *Anal.* ($C_{16}H_{17}NO_3S$) N, S.

2′-(*p*-Anisidino)acetophenone (16).—The sulfoxide **13** (30.3 g, 0.1 mol) in 1400 ml of THF and 160 ml of H_2O was stirred at 10–15° with 27 g of Al–Hg for 30 min.[17] This period was required for disappearance of sulfoxide (tlc). Filtration of the suspension, concn of the filtrate, and recrystallization of the residue (*i*-PrOH) afforded 18.5 g (77%), mp 66–67°. *Anal.* ($C_{15}H_{15}NO_2$) C, H, N.

Condensation of Benzaldehyde with 16.—The ketone **16** (2 g, 0.0083 mol) in 55 ml of abs EtOH containing 5 ml of 2 *N* $NaOCH_3$ in MeOH and 1 ml of PhCHO was left at room temp for 3 days. The product (2.5 g, 92%) sepd as orange crystals, mp 180–185°. It was recrystd once from *n*-BuOH and twice from C_6H_6–hexane to give 0.65 g (24%) of yellow crystals, mp 185–186° *Anal.* ($C_{22}H_{19}NO_2$) C, H, N.

Treatment with acid or heating failed to alter significantly the composition of the product as judged by its nmr spectrum. Reduction with LAH–$AlCl_3$ gave a mixture in which **8** could be detected by tlc. Strong absorption in the 3-μ region suggested the presence of open-chain product.

Ethyl 1-(*p*-Methoxyphenyl)-2-phenyl-4(1*H*)-quinolone-3-carboxylate (12).—Ethyl benzoylacetate (17.3 ml, 0.1 mol) was added to 0.104 mol of dimsyl sodium[17] in 60 ml of DMSO at 15°, followed in a few minutes by 26.9 g (0.1 mol) of the anhydride **11** in 50 ml of DMSO. The mixture was warmed slowly to 50° and, after gas evolution ceased, was kept at 70° for 1 hr. The product crystallized from the reaction soln overnight at room temperature: yield 32 g (80%); mp 242–243°. It was recrystd from C_6H_6–cyclohexane, mp 246–247°. *Anal.* ($C_{25}H_{21}NO_4$) C, H, N.

***o*-(Acetophenyl)-*N*-(*p*-methoxyphenyl)benzimidate (15).**—This compd was prepared from *N*-(*p*-methoxyphenyl)benzimidoyl chloride[4] and *o*-hydroxyacetophenone by the procedure described for the prepn of *p*-fluorophenyl *N*-(*p*-fluorophenyl)benzimidate:[18] yield 64%; mp 127–129°. It was recrystd from abs EtOH, mp 129–131°. *Anal.* ($C_{22}H_{19}NO_3$) C, H, N.

1-(*p*-Methoxyphenyl)-2-phenyl-4(1*H*)-quinolone (14). A. By Pyrolysis of 15.—A stirred 100-g sample of **15** was heated under N_2 to 250° where an exothermic reaction occurred. The temperature rose to 300°. It was allowed to fall to 250° and was kept there for 30 min. The product was decolorized with charcoal in hot EtOH to give 62 g (65%) of light orange needles, mp 198–200°. Recrystallization (EtOH) raised the melting point to 202–204°. *Anal.* ($C_{22}H_{17}NO_2$) C, H, N.

B. By Hydrolysis and Decarboxylation of 12.—The ester **12** (2 g, 0.005 mol) was refluxed with 3.5 ml of 35% NaOH in 30 ml of EtOH for 30 min. Concentration and acidification of the reaction mixture gave 1.81 g (98%) of 1-(*p*-methoxyphenyl)-2-phenyl-4-(1*H*)-quinolone-3-carboxylic acid, mp 263° dec. *Anal.* ($C_{23}H_{17}NO_4$) C, H, N. This acid (1.12 g) was heated at 280° for 10 min to yield 0.80 g (82%) of crystals, mp 197–198°, identical (ir) with a sample prepared by pyrolysis of **15**.

C. By Cyclization of 13.—A soln of 0.91 g (0.003 mol) of **13** in 8 ml C_6H_6, 0.3 ml of PhCHO, and 3 drops of piperidine was refluxed for 8 hr. The reaction mixture was concd and the residue crystd (EtOH); 0.77 g (79%); identical with the product from the pyrolysis of **15** (mp, mmp, and ir).

Table II

	Compound	Mp, °C	Formula[c]
8,	R′ = $CH_2CH_2NEt_2$[a]	137–138.5	$C_{27}H_{32}N_2O \cdot C_6H_{13}NO_3S$
8,	R′ = CH_2CH_2N⟨⟩[a]	164–167	$C_{27}H_{30}N_2O \cdot C_6H_{15}NO_3S$
25,	R′ = $CH_2CH_2NEt_2$[b]	123–124	$C_{26}H_{28}N_2O \cdot C_7H_8O_3S$
23,	R′ = CH_2CH_2N⟨⟩[a]	152.5–153.5	$C_{23}H_{26}N_2O \cdot C_6H_{13}NO_3S$
26,	R′ = $CH_2CH_2NEt_2$[b]	131–132	$C_{27}H_{30}N_2O_2 \cdot C_7H_8O_3S$

[a] Cyclohexanesulfamic acid salt. [b] *p*-Toluenesulfonic acid salt. [c] All compounds were analyzed for C, H, N.

2-Chlorodihydrochalcone (18).—2-Chlorochalcone[19] (97.1 g) in 800 ml of abs EtOH was shaken with Raney Ni and H_2 at 11.6 kg/cm² at room temp. H_2 (1 mol-equiv) was absorbed during 1.5 hr. The product crystallized from hexane to give 73.5 g (75%) of **18**, mp 44–45° [lit[19] mp 46.5°].

***N*-[3-(*o*-Chlorophenyl)-1-phenylpropyl]-*p*-anisidine (20).**—The crude *p*-methoxyanil **19** prepared from **18** (78 g, 0.2 mol) by the procedure of Grewe, *et al.*,[20] was not characterized but reduced directly by refluxing for 3 hr with 15 g (0.384 mol) of LAH in 650 ml of THF. The product, 34.8 g (50%), bp 206–214° (0.05 mm), crystallized at room temp (89% **20** by glpc). This compd was characterized as the **hydrochloride**, mp 214–215° (*i*-PrOH–Et_2O). *Anal.* ($C_{22}H_{22}ClNO \cdot HCl$) C, H, N.

1-(*p*-Hydroxyphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (23).—A soln of 21.6 g (0.1 mol) of 2-(2-oxocyclohexyl)acetophenone[21] and 10.9 g (0.1 mol) of *p*-aminophenol in 60 ml of AcOH was refluxed for 0.5 hr. The product sepd from the cooled reaction mixture: yield 25.6 g (89%), mp 181–182° (*i*-PrOH); uv (95% EtOH) λ_{max} 228, 298 mμ (ϵ16,100, 15,230); nmr ($CDCl_3$) δ 6.5–7.16 (m, 9, aromatic H), 6.18 (s, 1, C_3**H**), 4.9 (s, 1, O**H**), 1.5–2.9 ppm [m, 8, (CH_2)$_4$]; *Anal.* ($C_{20}H_{19}NO$) C, H, N.

1-(*p*-Hydroxyphenyl)-2-phenylindole (25).—A soln of 20.9 g of **23** in 1900 ml of xylene was stirred at reflux with 35 g 10% Pd–C under N_2 for 6 hr. Concentration of the filtered mixture and recrystallization (C_6H_6–cyclohexane) yielded 18.5 g (89%) of the dehydrogenation product: mp 139–140°; uv (95% EtOH) λ_{max} 223 (sh), 247 (sh), 300 mμ (ϵ24,400, 20,100, 19,800); nmr ($CDCl_3$) δ 6.5–7.16 (m, 14, aromatic H), 4.83 ppm (s, 1, O**H**). *Anal.* ($C_{20}H_{15}NO$) C, H, N.

2-(5-Methoxy-2-cyclohexanon-1-yl)acetophenone (22).—The undistilled pyrrolidine enamine prepared from 83.3 g (0.65 mol) of 4-methoxycyclohexanone[22] was stirred at reflux for 3 hr with 130 g (0.65 mol) of 2-bromoacetophenone in 1 l. of toluene. The pptd solid was collected, washed (Et_2O), and suspended in 250 ml of hot H_2O. The oil which formed was extracted ($CHCl_3$). Concentration of the dried extracts and distillation gave 82.7 g (67%) of a light yellow oil: bp 156–157° (0.06 mm); $n^{25}D$ 1.541. *Anal.* ($C_{15}H_{18}O_3$) C, H.

1-(*p*-Hydroxyphenyl)-5-methoxy-2-phenyl-4,5,6,7-tetrahydroindole (24).—A soln of 24.6 g (0.1 mol) of **22** and 10.9 g (0.1 mol) of *p*-aminophenol in 60 ml of HOAc was refluxed for 30 min and diluted with 30 ml of H_2O. The pptd product was recrystd from MeOH to give 27.4 g (86%) of **24**: mp 174–175°; uv (95% EtOH) λ_{max} 229, ϵ 294 mμ (ϵ 15,900, 15,100); nmr ($CDCl_3$) δ 6.1–7.16 (m, 11, aromatic H and O**H**), 3.7 (m, 1, OC**H**), 3.41 (s, 3, OCH_3), 1.7–3.4 ppm [m, 6, (CH_2)$_3$]. *Anal.* ($C_{21}H_{21}NO_2$) C, H, N.

1-(*p*-Hydroxyphenyl)-5-methoxy-2-phenylindole (26).—The tetrahydroindole **24**, 27.4 g, was heated with 20 g of 10% Pd–C in 500 ml of refluxing mesitylene for 3 days: yield 21.1 g (78%); mp 195–198° ($CHCl_3$–CCl_4 1:1). Two recrystallizations (*i*-PrOH) raised the melting point to 201–202°: uv (95% EtOH) λ_{max} 224 (sh), 247, 303 mμ (ϵ 31,700, 17,700, 21,400); nmr ($CDCl_3$) δ 6.5–7.33 (m, 13, aromatic H), 6.01 (s, 1, O**H**), 3.83 ppm (s, 3, OCH_3). *Anal.* ($C_{21}H_{17}NO_2$) C, H, N.

Preparation of Basic Ethers.—The basic ethers were prepared by known methods and are reported in Table II.

(15) We are indebted to Dr. Roman R. Lorenz for the KOH demethylation procedure and the characterization of the hydrochloride.

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Biological Activity

The estrogenic and antiestrogenic activities of these compounds were assessed on the basis of stimulation of the growth of the uterus of immature female rats. The test compounds were given by gavage either alone or in combination with estradiol (0.002 mg/kg per day) administered subcutaneously. On the 4th day the uteri were excised, blotted dry, and weighed. The antifertility activity was determined by administering the compound by gavage to mature female rats for 6 days beginning the morning after a proven insemination. The rats were autopsied 9 days after the last medication and their uteri were removed and examined for implantation sites and gross abnormalities.

Synthesis and Antiarrhythmic Activity of Naphthylalkylamines

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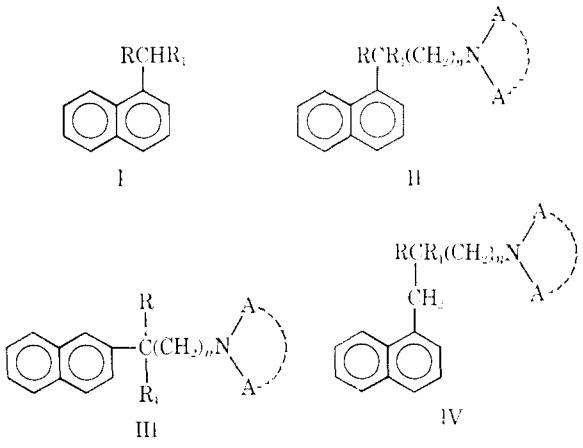
A further series of naphthylalkylamines was prepared and assayed for antiarrhythmic activity. Many of the compounds were found to be active *in vitro*, but only for five of them was activity confirmed *in vivo*. Comparative regression line analysis revealed that among the naphthylalkylamines so far investigated for antiarrhythmic activity, 1,5-dimorpholino-3-(α-naphthyl)pentane is still the most interesting one.

Our finding[1] that some α-naphthylalkylamines, especially 1,5-dimorpholino-3-(α-naphthyl)pentane, possess marked antiarrhythmic activity led us to extend this investigation to 83 chemically related compounds. The new naphthylalkylamines had the general structures I–IV, in which R was an alkyl or aminoalkyl group; R_1 was a primary amino or aminomethyl group; NAA was a tertiary amino group; $n = 2$–4.



Naphthylalkylamines with $R_1 = NH_2$ were prepared from the corresponding amides by the Hofmann reaction. Reduction of the related nitriles with excess LAH in Et_2O afforded naphthylalkylamines with $R_1 = CH_2NH_2$, reaction time and excess LAH depending on the steric hindrance of the nitriles.

Pharmacology.—All of the substances listed in Table II were submitted to the *in vitro* antiarrhythmic test, using quinidine and 1,5-dimorpholino-3-(α-naphthyl)pentane as reference standards. Many of them considerably reduced the maximal rate of stimulation of electrically driven isolated guinea pig auricles but did not inhibit the amplitude of contractions. These results are included in Table II in terms of relative potency, which was calculated from ED_{35} values as previously described[2] and expressed in relation to the antiarrhythmic activity of quinidine, which has been assigned the potency of 1.0.

Due to the promising results *in vitro*, all of the above compounds were tested subcutaneously in rats for the action on arrhythmias induced by $CaCl_2$. The procedure was essentially the same as previously described,[2] except that 120 mg/kg of $CaCl_2$ was infused. Reference standards and expression of results were as *in vitro*. Of all the tested substances, only **51**, **64**, **82**,

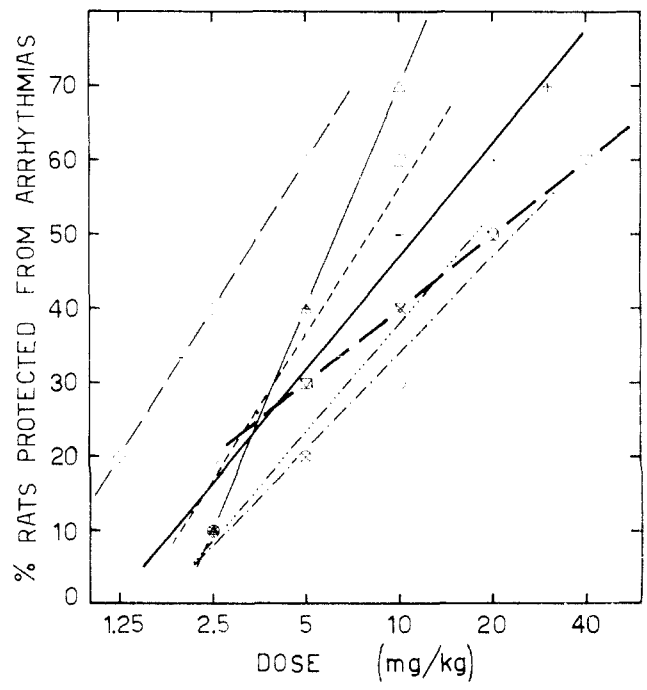


Figure 1.—$CaCl_2$-induced arrhythmias in rats. Regression lines of: **51** (△—△); **64** (○- - - -○); **82** (□- - - - -□); **84** (◇—◇); **120** (×- - - - -×); 1,5-dimorpholino-3-(α-naphthyl)pentane) (+—+); and quinidine (▽- - - -▽).

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