was cleaved with HIO<sub>4</sub>, the aldehyde was oxidized with Jones reagent, the acetoxyl group was saponified, and the hydroxy acid was converted to the lactone XIV, yield 21 mg of crude product;  $\nu_{\rm max}$  1712, 1738, 1770 cm<sup>-1</sup>. The material was purified by preparative tlc and the pure material which could not be obtained crystalline possessed the identical spectral properties of the crude material. The spectral and chromatographic properties of the

products could be due to the stereochemistry of the lactone and/or the configuration of C-5. Acknowledgment.—The authors are indebted to the

Acknowledgment.—Ine authors are indebted to the Syntex Corp. for their generous contribution of the starting 19-hydroxy steroids used in this study.

## Synthesis of Hormone Analogs Containing the *p*-Hydroxybenzyl Group

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A series of 1-(p-hydroxybenzyl)naphthalene, 1-(p-hydroxybenzyl)indan, and 4-(p-hydroxybenzyl)chroman derivatives was made for study as endocrine agents. These compounds were synthesized by reaction of substituted benzylmagnesium chlorides with appropriate methoxy or acetoxy ketones followed by transformations of the functional groups. Several of the compounds which contained two hydroxy or acetoxy groups were anti-gonadotropic and weakly estrogenic.

The present work is intended to provide a series of compounds which retain the approximate molecular size and functional group spacing of known estrogens but differ in conformation and flexibility. Although work toward this goal has been reported,<sup>2,3</sup> structures which meet the requirement by having a *p*-hydroxybenzyl group bonded to the 1 position of a bicyclic nucleus such as I have remained unavailable.

The desired compounds were synthesized by condensing substituted benzyl Grignard reagents with appropriate indanones, tetralones,<sup>4</sup> and chromanones as shown in Scheme I, followed by dehydration and hydrogenation. Precautions were taken in the preparation of the Grignard reagents to prevent coupling;



namely, high dilution and slow addition of the halide to a large excess of magnesium having a large surface area.<sup>5</sup>

In only two cases (IIa and IIb) could the tertiary alcohols (II) be purified. They were obtained by mild decomposition of the Grignard complex with ice water. The tertiary alcohols readily dehydrated to give the unsaturated compounds III (Table I). In the sixmembered ring compounds a mixture of *exo* and *endo* double-bond isomers was obtained. In one instance (IIIg) only the exocyclic isomer was isolated; however,

(1) To whom inquiries should be addressed.

(2) Cf. J. Grundy, Chem. Rev., 57, 281 (1957); R. E. Juday, D. P. Page, and G. A. Du Vall, J. Med. Chem., 7, 519 (1964); J. Bascoul and A. C. De Paulet, Compt. Rend., C264, 629 (1967).

(3) D. M. Lynch and W. Cole, J. Org. Chem., 31, 3337 (1966).

(4) For a paper dealing with the condensation of benzylmagnesium chloride with tetralones see H. A. Fahim, A. M. Fleifel, and F. Fahim, *ibid.*, **25**, 1040 (1960).

(5) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, J. Am. Chem. Soc., 70, 2296 (1948). When the Grignard reaction started at the onset of addition of the halide, no coupling product was detected.

an nmr spectrum on crude material from the mother liquor revealed the presence of some of the *endo* isomer. In the case of IIIe a pure sample of the *exo* isomer was obtained by fractional crystallization.

Identification of the isomers was based in part on their different vinyl hydrogen absorptions in the nmr spectra. The endocyclic isomers of the hydronaphthalene compounds have vinyl hydrogen signals at about 340 cps with a side-chain methylene signal at about 224 cps that is partly hidden by aromatic methoxy signals. The vinyl hydrogens of the exocyclic isomers appear at or above 400 cps.

The nmr spectrum of 7-methoxy-4-(p-methoxybenzylidene)chroman (IIIg) was studied further because of the questionable assignment of two protons which absorbed in the region of 380–400 cps. The overlap of signals in this region gave rise to an apparently inconsistent coupling pattern. In order to assign these protons and to verify the low-field absorption of the vinyl proton, a spectrum at 100 Mc was obtained. This spectrum clearly indicated that the 380-400-cps absorption at 60 Mc was due to the  $C_6$  and  $C_8$  aromatic hydrogens. The C<sub>6</sub>-H is coupled  $(J_o = 8.5 \text{ cps})$  with the C<sub>5</sub>-H (which is centered at 452 cps at 60 Mc) and also with the C<sub>8</sub>-H ( $J_m = 2.5$  cps). The remaining absorption in the aromatic region is the vinyl hydrogen absorption at about 414 cps (60 Mc), which is split (J = 1.5 cps) by the allylic methylene group, and the  $A_2B_2$  pattern of the aromatic hydrogens of the pmethoxybenzylidene group. The absence of endocyclic vinyl hydrogen absorption (at about 313 cps on the 60-Mc spectrum) and the presence of two  $CH_2$  triplets (centered at 172 and 249 cps, J = 5.5 cps; 60-Mc spectrum) definitely confirm the exocyclic structure for IIIg.

In contrast with the six-membered ring cases, the indanones gave isolable products (IIIa and IIIb) in which the double bond is exocyclic.<sup>6,7</sup> The nmr spectra

<sup>(6)</sup> One nmr spectrum of IIIb taken in CDCl<sub>3</sub> showed some endocyclic isomer (vinyl hydrogen, 363 cps). This was shown to be due to isomerization caused by acid in the CDCl<sub>3</sub>, since a spectrum of IIIb taken in CDCl<sub>3</sub> stored over Na<sub>2</sub>CO<sub>3</sub> showed no trace of the *endo* isomer. For this reason Na<sub>2</sub>CO<sub>3</sub>-treated CDCl<sub>5</sub> has been used to record the nmr spectra reported in this paper.

<sup>(7)</sup> The condensation of  $\gamma$ -picoline with indanones also gave products having the exocyclic double bond, while the condensation of  $\gamma$ -picoline with tetralones gave products containing both double-bond isomers. See ref 3.



show vinyl hydrogen absorption above 400 cps (exocyclic double bond) and two  $CH_2$  groups whose protons have equivalent chemical shifts, giving rise to a fourproton singlet at 182 cps. An nmr spectrum of the residue from the mother liquors of IIIa did show evidence of the endocyclic isomer with vinyl hydrogen absorption at 361 cps.

The unsaturated compounds III afforded an opportunity to compare the relative stability of the *exo/endo* double-bond isomers for the five-membered and sixmembered ring cases. The *exo*  $\rightleftharpoons$  *endo* equilibrium compositions were measured for two cases (IIIa and IIIe). Equilibrium was established at 110° in refluxing toluene solution with *p*-toluenesulfonic acid during 2 hr, followed by neutralization with aqueous Na<sub>2</sub>CO<sub>3</sub> and product analysis using gas-liquid partition chromatography and nmr.

In the case of IIIa the equilibrium composition consisted of 95% exo and 5% endo;  $\Delta F = 2.24$  kcal/mole. An additional equilibration for 17 hr gave the same ratio of isomers as obtained from the 2-hr treatment.

In the case of IIIe the equilibrium was approached from both sides, starting first with the pure *exo* isomer IIIe and then with a sample which was enriched in the *endo* isomer. Both gave the same result: 20% exo, 80%*endo*;  $\Delta F = -1.06$  kcal/mole.

Compounds IIIa, IIIb, and IIIg had predominately the exocyclic double-bond structure. These results were particularly interesting since, in simple systems which do not have the conjugative electronic and steric effects present in our systems, the endocyclic double-bond isomers have been found to be more stable in both fiveand six-membered rings.<sup>8</sup>

Only one form of each exocyclic double bond compound was detectable, even though *cis-trans* isomers are theoretically possible. The low-field vinyl hydrogen absorptions in the nmr give support to the view that these compounds have the less hindered *trans* stereochemistry. This conclusion is also strengthened by comparing their uv spectra with those of *cis*- and *trans*-4,4'-dimethoxystilbene.<sup>9</sup> Compound IIIa has  $\lambda_{\max}^{\text{EtOH}}$  344 m $\mu$  (shoulder,  $\epsilon$  22,600), 331 (29,700), 307 (shoulder, 25,200), 295 (25,900); IIIe exocyclic isomer has  $\lambda_{\max}^{\text{EtOH}}$  320 m $\mu$  (shoulder,  $\epsilon$  21,000), 297 (26,000), 230 (shoulder, 10,000), 210 (25,000).

Reactions of the type illustrated in Scheme II were used in preparing the compounds listed in Tables I and II. Demethylation of the methyl ethers with pyridine hydrochloride at 200–210° under  $N_2$  gave fairly good yields of the phenols except for two cases. Demethylations of IIIb and IIIg, each containing several ether linkages, failed to give clean products. However, their more saturated analogs, VIb and VIg, were successfully demethylated.

Where mixed functional groups were desired, the method of blocking a phenol group as the benzyl ether was used. Thus hydrogenation of IIIf was accompanied by hydrogenolysis of the benzyl group, giving

 <sup>(8)</sup> E. Gil-Av and J. Shabtai, *Chem. Ind.* (London), 1630 (1959); A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, Z. Jacura, J. Am. Chem. Soc., 81, 3153 (1959).

<sup>(9)</sup> J. Derkosch and G. Friedrich, Monatsh. Chem., 84, 1146 (1953).



<sup>a</sup> In compounds of structure B a mixture of endocyclic and exocyclic double-bond isomers is present. <sup>b</sup> A, acetone; B, benzene; Et, ethanol; EA, ethyl acetate; H, hexane. <sup>c</sup> The yields of compounds III are based on the starting ketone unless otherwise stated. <sup>d</sup> A cloudy melt was obtained that became clear at 150<sup>c</sup>. <sup>e</sup> Based on the tertiary alcohol IIa. <sup>f</sup> A pure sample of the *exo* isomer was obtained by fractional crystallization, mp 113–115<sup>c</sup>; the best sample of the *endo* isomer had mp 70–72<sup>c</sup> but contained 14% of the *exo* isomer (by gas chromatography). <sup>e</sup> An nmr spectrum on a trace of solid (mp 90–113<sup>c</sup>) from the mother liquors of IIIg indicated the presence of some of the *endo* isomer. <sup>h</sup> This compound was used in the next step without purification. <sup>i</sup> A cloudy melt was obtained that cleared up at 168<sup>c</sup>. <sup>j</sup> Based on crude IVc. <sup>k</sup> All compounds were analyzed for C and H except IVc, which was used in the next step without purification.



Compd	Structure	R	R'	B''	Crystn solvents <sup>a</sup>	% vield	Mn or hn (mm) °C	Formula
VIa	D	0CH	u	OCH .	E+	70 J1610	69 70	C II O
via	D	00113	п		Et.	04	08-70	$C_{18} r_{20} O_2$
b	D	$OCH_3$	$OCH_3$	OCH3	$\mathbf{Et}$	85	75-77	$C_{19}H_{22}O_3$
с	$\mathbf{E}$	H		$OCH_3$		80	135(0.1)	$C_{18}H_{20}O$
d	$\mathbf{E}$	$OCH_3$		Н		81	125 - 137 (0.16)	$C_{18}H_{20}O$
е	$\mathbf{E}$	$OCH_3$		$OCH_3$	$\mathbf{Et}$	80	$46 - 48^{b}$	$\mathrm{C}_{19}\mathrm{H}_{22}\mathrm{O}_{2}$
f	$\mathbf{E}$	$OCH_3$		OH	Et-H	85	102 - 105	$\mathrm{C}_{18}\mathrm{H}_{20}\mathrm{O}_2$
g	$\mathbf{F}$	$OCH_3$		$OCH_3$		87	164(0.16)	$\mathrm{C}_{18}\mathrm{H}_{20}\mathrm{O}_{3}$
$\mathbf{h}$	$\mathbf{E}$	OAc		OH	В	33	127 - 130	$C_{19}H_{20}O_{3}$
VIIa	D	OH	н	OH	E–B	78	159 - 162	$C_{16}H_{16}O_2$
b	D	OH	OH	OH	Et-B-H	77	162 - 164	$C_{16}H_{16}O_3$
С	$\mathbf{E}$	н		OH		68°		$C_{17}H_{18}O$
d	$\mathbf{E}$	OH		н		87°		$C_{17}H_{18}O$
е	$\mathbf{E}$	OH		OH	B-H	68	130-132	$C_{17}H_{18}O_2$
f	$\mathbf{F}$	OH		OH	С	22	127 - 129	$C_{16}H_{16}O_3$
VIIIa	D	OAc	$\mathbf{H}$	OAc	B-H	85	64 - 66	$\mathrm{C}_{20}\mathrm{H}_{20}\mathrm{O}_4$
b	D	OAc	OAc	OAc	B-H	77	130-132	$\mathrm{C}_{22}\mathrm{H}_{22}\mathrm{O}_6$
с	$\mathbf{E}$	$\mathbf{H}$		OAc		73ª	147 - 154(0.1)	$C_{19}H_{20}O_2$
d	$\mathbf{E}$	OAc		$\mathbf{H}$		83*	155-162(0.2)	$C_{19}H_{20}O_{2}$
е	$\mathbf{E}$	OAc		OAc	B-H	93	89-92	$C_{21}H_{22}O_4$
f	$\mathbf{E}$	$OCH_3$		OAc	B-H	84	50 - 52	$C_{20}H_{22}O_3$
g	$\mathbf{E}$	OCOPh		OCOPh	B-H	77	152 - 155	$C_{31}H_{26}O_4$
h	$\mathbf{F}$	OAc		OAc	B-H	77	117-118	ConHood

<sup>a</sup> C, CHCl<sub>3</sub>; E, Et<sub>2</sub>O; see ref b in Table I. <sup>b</sup> A cloudy melt was obtained that cleared up at  $60^{\circ}$ . <sup>c</sup> This compound was used in the next step without purification. <sup>d</sup> Based on crude IVc. <sup>e</sup> Based on crude IVd. <sup>f</sup> All compounds were analyzed for C and H except VIIc and VIId, which were used without purification.

the methoxyphenol VIf. Likewise IIIh gave VIh. The preparation of the acetoxybenzyl ether IIIh was difficult, because the condensation of *p*-benzyloxybenzylmagnesium chloride with 6-acetoxy-1-tetralone gave a product containing recovered ketone. It was necessary to saponify, separate the phenols, and reacetylate. Apparently enolization (in the presence of the Grignard reagent) is a serious side reaction with 6-acetoxy-1tetralone but not with 6-methoxy-1-tetralone.

From measurements of molecular models of these compounds it appears that the exocyclic double-bond compounds IVa and IVb are fairly rigid molecules having oxygen-oxygen spacing of about 12 Å. The *endo* isomer of IVb and also the dehydrogenation product X are more flexible but may assume planar shapes having the same oxygen-oxygen spacing. The reduced products (VIIIa, b, e, and f) cannot become planar, are somewhat flexible, but may have also the same maximum oxygen-oxygen spacing of about 12 Å.

These compounds were tested by Dr. R. E. Mauer and associates<sup>10</sup> for estrogenic effects using the rat uterine growth test<sup>11</sup> with estradiol as a positive reference. All of the compounds were inactive or very low in estrogenic activity. Those which had measurable estrogenic activity were Va (0.003%) of estradiol activity), Vd (0.02%), VIIe (0.006%), and VIIIe (0.07%).

Most of the compounds were tested also qualitatively for antigonadotropic activity using the parabiotic rat assay<sup>12</sup> with testosterone as a positive reference. Compounds which showed activity were IVa, Va, Vd, VIh, VIIe, VIIIb, VIIIe, VIIIh, and XI. It was apparent that there exists in this series, as in the natural compounds, an appreciable correlation between the estrogenic effect and the antigonadotropic activity.

## **Experimental Section**

Melting points are corrected; boiling points are uncorrected. Ir spectra were recorded by Mr. W. H. Washburn and associates on a Perkin-Elmer Model 421 or 521 grating spectrophotometer in CHCl<sub>3</sub>, and nmr spectra by Mrs. R. S. Stanaszek, Mr. R. S. Egan, and Dr. M. Levenberg. Unless otherwise specified, umr data were obtained using a Varian A-60 instrument in CDCl<sub>3</sub>, and values are in cps downfield from TMS. The CDCl<sub>3</sub> was stored over Na<sub>2</sub>CO<sub>3</sub>.<sup>6</sup> Catalytic reductions were performed by Messrs. M. Freifelder and D. Dunnigan, and the and glpe by Mrs. Evelyn Baker and associates. Uv spectra were recorded by Messrs. J. Sutherland and D. Williamson. Microanalyses were by Mr. V. Rauschel and his staff. Where analyses are indicated only by symbols of the elements, analytical results obtained were within  $\pm 0.4\%$  of the theoretical values.

1,2,3,4-Tetrahydro-6-methoxy-1-(p-methoxybenzyl)-1-naphthol (IIb). General Method for IIa and IIb.—A solution of 5.1 g of anisyl chloride<sup>13</sup> in 40 ml of dry Et<sub>2</sub>O was added, under N<sub>2</sub>, with rapid stirring to a mixture of 35 ml of dry Et<sub>2</sub>O, 3 g of Mg turnings, and 3 g of Mg powder (40 mesh) over a period of 3.25 hr. This mixture was then cooled in an ice bath and 5 g of 6-methoxy-1-tetralone dissolved in 60 ml of dry C<sub>6</sub>H<sub>6</sub> was added over a 10-min period. Following 18 hr of stirring at room temperature under N<sub>2</sub>, the reaction mixture was decanted from excess Mg onto ice. The gel which formed was removed by suction filtration and washed well with ether. The ether solution from the filtrate was washed (H<sub>2</sub>O, NaCl), dried (MgSO<sub>4</sub>), and taken to dryness *in racuo* at room temperature. Crystallization from benzenehexane at 4° provided 5.15 g of white crystals, mp 70–73°,  $\nu_{\rm max}$  3585 cm<sup>-1</sup>. Anal. (C<sub>19</sub>H<sub>22</sub>O<sub>8</sub>) C, H.

In the same manner benzylmagnesium chloride gave an 88°  $_{\ell}$  yield of 1,2,3,4-tetrahydro-6-methoxy-1-benzyl-1-naphthol (IIa), mp 64.5-67.5°. Anal. (C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>) C, H.

3,4-Dihydro-6-methoxy-1-(p-methoxybenzyl)naphthalene and 1,2,3 4-Tetrahydro-6-methoxy-1-(p-methoxybenzyliden e) n a p hthalene (IIIe). General Method for IIIa-g.-5-Methoxy-1indanone,145.6-dimethoxy-1-indanone,15 and 7-methoxy-4-chromanone<sup>16</sup> were prepared by methods described in the literature. Other ketones were purchased. The Grignard procedure described above was followed except that after addition of the ketone the mixture was stirred under reflux for 3 hr and then decomposed with ice and NH<sub>4</sub>Cl solution. Work-up via ether extraction provided a yellow-orange oil. This oil was heated in a distillation apparatus until the vapor temperature reached 100° (0.4 mm). Crystallization of the residue from EtOH afforded white crystals, mp 60-84°.17 A rough estimate based on the nmr spectrum of this material indicates a 60:40 endo:exo ratio. Thin layer chromatography on silica gel revealed two spots with  $R_{\rm f}$  values of 0.74 for the *endo* isomer and 0.76 for the *exo* isomer on development with ammonium molybdate. Compounds IIIb, IIIe, and IIIf were prepared in this way except that in the case of IIIf THF was used instead of ether (because of the low solubility of p-benzyloxybenzyl chloride in  $Et_2O$ ), the excess Grignard reagent was carbonated with Dry Ice, and the resulting acid was removed by extraction. The Grignard reagent for the latter reaction was prepared from commercial p-benzyloxybenzyl chlo- $\mathrm{ride.^{18}}$ 

Alternatively, the crude tertiary alcohols prepared by the method described for IIb were dehydrated by refluxing a solution of 0.19 mole of the alcohol and 80 mg of *p*-toluenesulfonic acid in 500 ml of toluene with a Dean-Stark trap for 1 hr. After removing the solvent at reduced pressure the residue was dissolved in  $Et_2O$ ,  $C_6H_6$  (for IIIg), or CHCl<sub>3</sub> (for IIIa) and the solution was washed with 5% NaHCO<sub>3</sub> solution, dried, and evaporated *in vacuo* to give the crude product. Compounds IIIa, IIIc, and IIIg were prepared in this way. Compound IIId was obtained in this way from the pure tertiary alcohol IIa.

**1,2,3,4-Tetrahydro-6-methoxy-1**-(*p*-methoxybenzyl)naphthalene (VIe). General Method for VIa-h. A 24.5-g sample of the mixture IIIe was hydrogenated at room temperature at 2.1-2.8 kg/cm<sup>2</sup> in Methyl Cellosolve with Pd -C. Removal of the catalyst and solvent provided, after crystallization, 19.4 g of white crystals of VIe: mp 46-48°:<sup>19</sup>  $\lambda_{\text{max}}^{\text{hoff}}$  285 m $\mu$  ( $\epsilon$  3280), 278 (3900), 229 (21,700). Hydrogenation with accompanying hydrogenolysis of IIIf gave VII:  $\nu_{\text{max}}$  3596, 3440 (broad), 1746 cm<sup>-1</sup>.

5,6,7,8-Tetrahydro-5-(*p*-hydroxybenzyl)-2-naphthol (VIIe). General Method for VIIa-f and IVa-d.—A mixture of 22.3 g of VIe and 67 g of pyridine hydrochloride was heated at 200-210° with stirring under N<sub>2</sub> for 1 hr. After cooling to room temperature the reaction mixture was dissolved in a solution of 28 g of NaOII in H<sub>2</sub>O (200 ml). This solution was washed with ether and acidified with cold 1:1 HCl. Work-up *via* ether extraction near-white solid: mp 130-132°:  $\nu_{max}$  3597, 3430 cm<sup>-1</sup> (broad).

In the preparation of VIIb, the reaction mixture was worked-up by dilution with water and ether extraction: VIIb is destroyed by base. Compound VIIf was prepared as described above except that after the reaction mixture was dissolved in NaOH solution, it was warmed on the steam bath for 1 hr (this treatment may be unnecessary). In the preparation of compounds IVd and VIIc the reaction mixture was acidified with 10% HCl in place of the NaOH treatment, and then extracted with ether.

Compounds IVc, VIIc, and VIId could not be extracted or were only incompletely extracted from ether with dilute NaOII

<sup>(10)</sup> Blological assays we e done under the direction of Dr. R. E. Mauur, Dr. A. I. Cohen, and Dr. R. Oslapas.

<sup>(11)</sup> H. D. Lauson, C. G. Heller, J. B. Golden, and E. L. Sevringhaus, *Endocrinology*, **24**, 35 (1939).

<sup>(12)</sup> R. Hertz and R. K. Meyer, *ibid.*, **21**, 756 (1937). See also R. I. Dorfman and F. A. Kincl, *Methods Hormone Res.*, **5**, 148 (1966).

<sup>(13)</sup> K. Rorig, J. D. Johnston, R. W. Hamilton, and T. J. Telinski, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 576.

<sup>(14)</sup> C. A. Panetta and S. C. Bunce, J. Ocg. Chem., 26, 4859 (1961).

<sup>(15)</sup> J. Koo, J. Am. Chem. Soc., **75**, 1891 (1953).

<sup>(16)</sup> J. D. Loudon and R. K. Razdan, J. Chem. Soc., 4299 (1954).

<sup>(17)</sup> See footnote f, Table I.(18) Aldrich Chemical Co., Inc., Milwaukee, Wis.

<sup>(19)</sup> See footnote b, Table II.

solution; they could be extracted with Claisen's alkali.<sup>20</sup> This was not attempted with IVd.

5 6,7,8-Tetrahydro-5-(p-hydroxybenzyl)-2-naphthol Diacetate (VIIIe). General Method for VIIIa-h and Va-d.—To a 10-g sample of VIIe dissolved in 170 ml of pyridine in a stoppered 500ml flask was added, dropwise with swirling, 40 ml of Ac<sub>2</sub>O. This solution was swirled for 10 min at room temperature and allowed to stand overnight. H<sub>2</sub>O (50 ml) was added dropwise to the swirled solution over a 15-min period with slight cooling in an ice bath. Further dilution gave an oil that was extracted (Et<sub>2</sub>O). The ether extract was washed (5% HCl, H<sub>2</sub>O, 5% Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O). After drying (MgSO<sub>4</sub>), the solvent was removed at reduced pressure to leave an oil which crystallized from benzene-hexane to give 12.4 g of white crystals, mp 89-92°,  $\nu_{max}$  1745 cm<sup>-1</sup>.

In the preparation of VIIIg, benzoyl chloride was substituted for Ac<sub>2</sub>O and work-up was via CHCl<sub>3</sub> extraction. This product, 5,6,7,8-tetrahydro-5-(p-hydroxybenzyl)-2-naphthol dibenzoate, showed  $\nu_{\rm max}$  1725 cm<sup>-1</sup>.

**6-Acetoxy-1-tetralone.**—Demethylation of 6-methoxy-1-tetralone by the method described for the preparation of IVd and VIIc (including separation from neutral material by extraction of the product from ether with 10% aqueous NaOH) provided a crude pink solid: mp 127–135° (lit.<sup>21</sup> mp 121.0–121.5°);  $\nu_{\rm max}$  3580, 3250 (broad), 1658 cm<sup>-1</sup>. This solid resisted purification. It was acetylated by the method described for the preparation of 6-acetoxy-1-tetralone as a colorless oil: bp 126–143° (0.16–0.17 mm) [lit.<sup>21</sup> 152–154° (1 mm)];  $\nu_{\rm max}$  1675, 1754 cm<sup>-1</sup>. Attempted crystallization failed; lit.<sup>21</sup> mp 62.5°, polymorph mp 42°.

5-(*p*-Benzyloxybenzyl)-7,8-dihydro-2-naphthol Acetate and 5-(*p*-Benzyloxybenzylidene)-5,6,7,8-tetrahydro-2-naphthol Acetate (IIIh).—The Grignard reagent (56 mmoles), prepared from *p*-benzyloxybenzyl chloride in the manner described above for IIIf, was added over a period of 1 hr and 10 min to a solution of 10 g (49 mmoles) of 6-acetoxy-1-tetralone in 100 ml of dry THF cooled in an ice-salt bath. The mixture was allowed to come to room temperature overnight with stirring under  $N_2$ . At this point a negative Gilman test<sup>22</sup> was obtained. Work-up with ice and aqueous NH<sub>4</sub>Cl gave about 23 g of an oil. An ir spectrum indicated the presence of some 6-acetoxy-1-tetralone. The oil was dissolved in 500 ml of toluene with 20 mg of *p*-toluenesulfonic

(20) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p 310.

(21) S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. N. Rzheznikov, and I. V. Torgov, *Tetrahedron*, **18**, 1355 (1962).

(22) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," 2nd ed, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1962, p 469.

acid and the solution was heated under reflux (Dean-Stark trap) for 1 hr. The toluene was removed at reduced pressure and replaced with ether. This solution was washed with NaHCO<sub>3</sub> and water, dried, and evaporated *in vacuo* to give about 20 g of a dark oil which could not be crystallized.

This oil was dissolved in 100 ml of 95% EtOH containing 5.5 g of KOH and this solution was heated under reflux for 1 hr, poured into H<sub>2</sub>O (500 ml), and extracted (Et<sub>2</sub>O) (an emulsion required that the mixture be centrifuged to effect separation of the layers). The ether extract was then extracted with Claisen's alkali,<sup>20</sup> washed well with water, and dried (MgSO<sub>4</sub>). Removal of the solvent at reduced pressure left 7 g of a semisolid yelloworange residue. The nmr and ir spectra of this material suggest that it is a mixture of benzyl *p*-tolyl ether and possibly *p*-benzyloxybenzyl alcohol. Work-up of the aqueous KOH solution by a dark red oil that partially solidified on standing but which could not be purified. Any 6-hydroxy-1-tetralone would be expected to be in this residue.

The Claisen's alkali extract upon similar work-up gave 5 g of a yellow-red oil that could not be induced to crystallize. Acetylation of this oil by the method described for the preparation of VIIIe provided 2.87 g of IIIh which separated from benzene-hexane as a near white powder, mp  $85-92^{\circ}$ ,  $\nu_{max}$  1748 cm<sup>-1</sup>.

**6-Methoxy-1-**(*p*-methoxybenzyl)naphthalene (IX).—An intimate mixture of 2 g of IIIe and 548 mg of sublimed sulfur was heated under N<sub>2</sub> at 205–210° for 5 hr. The mixture was cooled, taken up in ether, and filtered with slight suction. The filtrate was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was decolorized with charcoal in EtOH giving, after two recrystallizations, 666 mg (34%) of white crystals: mp 97–100°;  $\lambda_{max}^{EtOH}$  331 m $\mu$  ( $\epsilon$  2570), 316 (1960), 296 (6160), 277 (7520), 231 (56,400). The nmr spectrum has a CH<sub>2</sub> singlet at 258 cps. *Anal.* (C<sub>19</sub>H<sub>18</sub>O<sub>2</sub>) C, H.

**5**-(*p*-Hydroxybenzyl)-2-naphthol (X) was prepared from IX by the pyridine hydrochloride method described for the preparation of VIIe. A 40% yield of X was obtained as a near-white solid from Me<sub>2</sub>CO-H<sub>2</sub>O; mp 191-194° (after drying *in vacuo* to remove acetone). *Anal.* (C<sub>17</sub>H<sub>14</sub>O<sub>2</sub>) C, H.

5-(*p*-Hydroxybenzyl)-2-naphthol Diacetate (XI).—Acetylation of X in the manner described for the preparation of VIIIe gave an 81% yield of XI as fine pale yellow crystals from benzene-hexane; mp 119.5–120.5°,  $\nu_{\rm max}$  1753 cm<sup>-1</sup>. Anal. (C<sub>21</sub>H<sub>18</sub>O<sub>4</sub>) C, H.

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## Potential Antitumor Agents. VI. Bisquaternary Salts

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Investigations of the structure-activity relationships of a series of bisquaternary ammonium heterocycles against the L1210 leukemia system are described.

In an attempt to delineate further the features essential for experimental antileukemic activity in this area the quaternary salts represented by I were prepared. These differed from our parent series, the quaternary salts of N,N'-(6-quinolyl)terephthalamide, in the reversal of an amide function. This series (I) covering a range of lipophilic-hydrophilic properties had no active members.

Previous work<sup>2</sup> had shown an enhancement of experi-

mental antileukemic effectiveness when intercharge separation was increased by a variety of means, provided



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<sup>(2)</sup> Part V: G. J. Atwell and B. F. Cain, J. Med. Chem., 10, 706 (1967)