# Benzospirans Bearing Basic Substitution. I. Spiro[cyclohexane-1,2′-indans]

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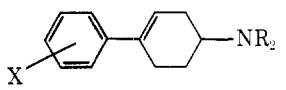
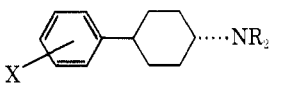
The carbanion obtained from the ethylene ketal of 4-carbomethoxycyclohexanone (LDA) was treated with benzyl chloride to give the corresponding 4-benzylated derivative. Protecting groups were removed and the resulting keto acid cyclized to spiro[cyclohexane-1,2′-indan]-1′,4-dione. This was converted in several steps to spiro[cyclohexane-1,2′-indan]-4-one. Preparation of analogues substituted by methoxyl in the aromatic ring is described. The ketone was transformed to the primary amine in several steps. Preparation of derivatives of the amines including the *p*-fluorobutyrophenones is described. Analogues containing hydroxy and exomethylene substituents in the five-membered ring were prepared by a modification of the synthesis. The stereochemistry of the *exo*-methylene compound is discussed.

We have reported earlier on the preparation and CNS activity of a series of derivatives of 4-arylcyclohex-3-enylamines (**1**)[1] and 4-arylcyclohexylamines (**2**).[2] The observation that the ortho-substituted derivatives (**1a,b, 2a,b**) in



**1a**, X = *o*-$CH_3$
**b**, X = *o*-$OCH_3$



**2a**, X = *o*-$CH_3$
**b**, X = *o*-$OCH_3$

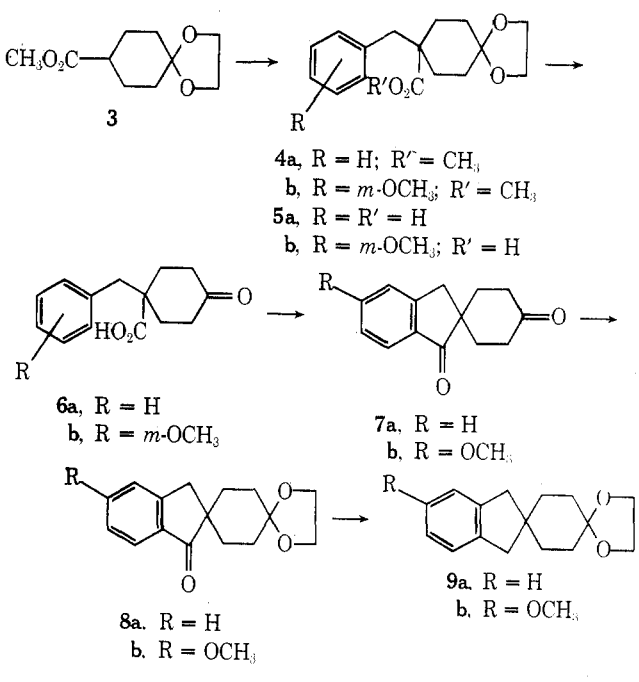
each series showed considerable biological activity was considered of particular interest; interaction of the ortho substituent with the equatorial proton on the adjacent alicyclic ring make it likely that the preferred conformation of these molecules is one in which the two rings are in some skewed arrangement. We thus decided to prepare analogues of those compounds in which those rings would be actually locked orthogonal to each other. The classic means for achieving this—at the cost of a slight increase in the ring to ring distance—lies in the preparation of the corresponding benzospirans.

The key to entry to the desired carbon skeleton was provided by the recently developed strong nonnucleophilic base, lithium diisopropylamide (LDA). Thus, treatment of the ethylene ketal (**3**) obtained from 4-carbomethoxycyclohexanone[3] with LDA followed by benzyl chloride afforded the alkylation product (**4a**) in good yield (Scheme I).

The highly hindered ester grouping of **4**, not surprisingly, proved refractory to saponification; the transformation was, however, achieved in good yield by means of sodium hydroxide in refluxing ethylene glycol. Deketalization of the crude acidic product (dilute hydrochloric acid in acetone) afforded the keto acid **6a**. Cyclization to the benzospiran skeleton (**7a**) was effected in modest yield by means of liquid hydrogen fluoride. The parent compound (**7a**) was accompanied by a trace of a product whose mass spectrum and elemental analysis suggested that the carbonyl group of the cyclohexane had reacted to form the corresponding difluoro derivative (**10**), an unusual reaction under the mild conditions employed.

Treatment of the diketone **7a** with 1 equiv of ethylene glycol under the usual conditions for ketalization went in straightforward manner to afford the monoketal **8a**; the ir spectrum of the product ($\nu_{max}$ 1690 $cm^{-1}$) confirms that the more reactive cyclohexanone carbonyl has in fact undergone reaction. Reduction of the free carbonyl group was then achieved by means of the Huang-Minlon modification of the Wolff–Kishner reaction. The amazingly simple NMR spectrum of the product, **9a**, which consists of but four singlets (ArH, $\delta$ 7.12, 4 H; ketal $\delta$ 4.0, 4 H; $ArCH_2$, $\delta$ 2.8, 4 H;

Scheme I



**3**

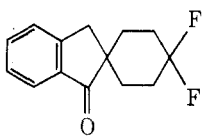
**4a**, R = H; R′ = $CH_3$
**b**, R = *m*-$OCH_3$; R′ = $CH_3$
**5a**, R = R′ = H
**b**, R = *m*-$OCH_3$; R′ = H

**6a**, R = H
**b**, R = *m*-$OCH_3$

**7a**, R = H
**b**, R = $OCH_3$

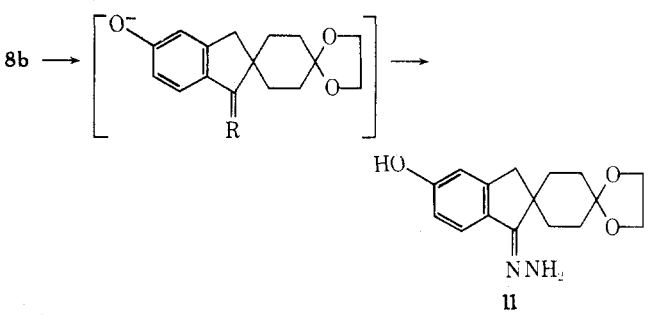
**8a**, R = H
**b**, R = $OCH_3$

**9a**, R = H
**b**, R = $OCH_3$



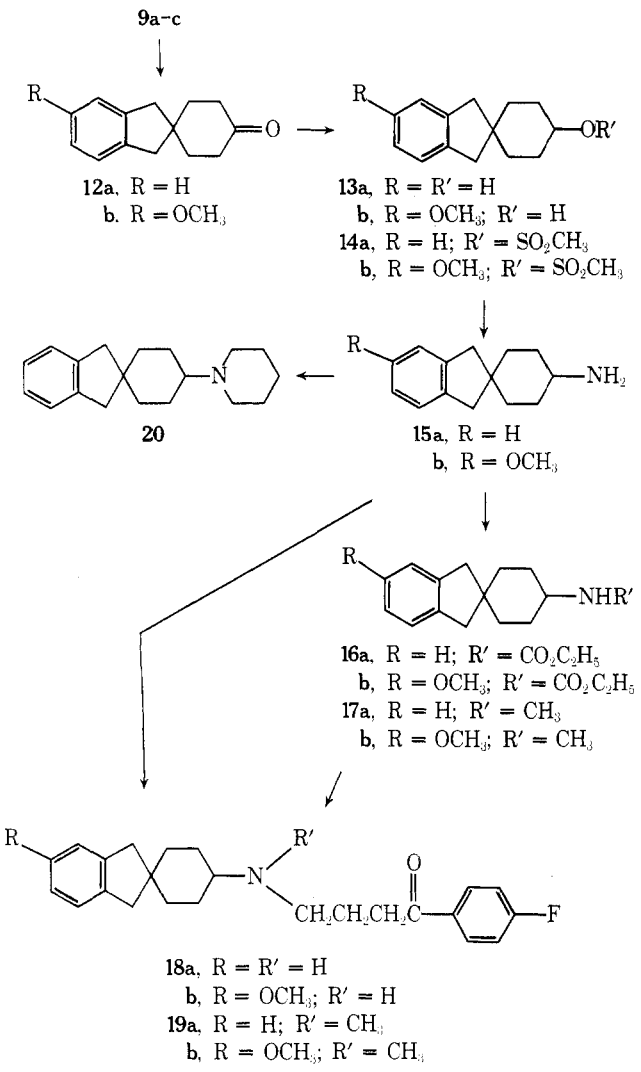
**10**

cyclohexane $CH_2$, $\delta$ 1.67, 8 H), at the same time confirms the structure of the product and attests to the high degree of symmetry of the molecule. The corresponding analogue substituted by methoxyl (**9b**) group was prepared in the same manner by using the meta-substituted benzyl chlorides in the initial alkylation step. Wolff–Kishner reaction of the methoxy analogue (**8b**) afforded the phenolic hydra-



**11**

Scheme II

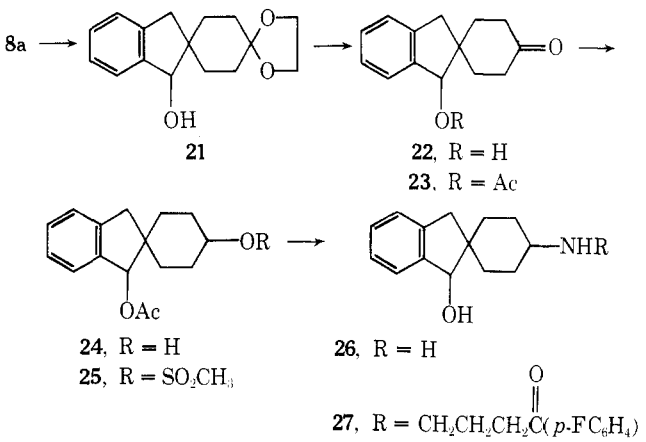



zone 11 in significant amounts. It is considered likely that some portion of the starting material or its hydrazone may undergo base-catalyzed ether cleavage under the strongly basic conditions;[4] the presence of the negative charge on the phenoxide may then inhibit formation of the hydrazine anion required for completion of the reduction.

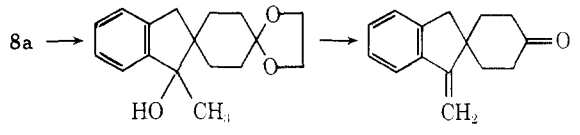
Removal of the ethylene ketal by means of dilute aqueous acid in acetone followed by reduction of the resulting ketones (**12a,b**) by means of sodium borohydride afforded the corresponding alcohols (**13a,b**) (Scheme II). These last were converted to the primary amines (**15a,b**) by a convenient three-step sequence which consists of conversion of the alcohol to its mesylate, displacement of the leaving group by means of sodium azide in DMF, and finally reduction of the crude azide with lithium aluminum hydride. Reaction of the parent amine **15a** with 1,5-diiodopentane gave the corresponding piperidine **20.**

Each of the primary amines was then converted to its carbamate by means of ethyl chloroformate. Reduction of these acylated products with lithium aluminum hydride gave the N-methylated analogues (**17a,b**). It has been frequently shown that central nervous system activity of amines is maximized by conversion of these to the *p*-fluorobutyrophenone derivatives.[5] Both primary and secondary amines were thus alkylated with the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone. Brief exposure of the alkylation product to aqueous methanolic acid afforded the butyrophenone derivatives (**18a,b, 19a,b**).

Turning our attention to the functionality present in the five-membered ring in one of the intermediates, we found the carbonyl group of **8a** to be surprisingly inert toward sodium borohydride. Reduction by means of lithium aluminum hydride afforded an oily alcohol, which was characterized as its crystalline acetate **23.** Reduction of the cyclohexanone obtained on deketalization (**23**) again afforded an oily product; both NMR and TLC suggested that this consisted largely of one of the two possible hydroxy acetates (syn and anti OH and OAc). Isolation of a homogeneous crystalline mesylate in 65% yield from treatment of the mixture with methanesulfonyl chloride in pyridine confirms the predominance of one isomer. It is, however, hazardous to assign configurations in this case without both isomers in hand.[6] The mesylate **25** was then taken on to the amine **26** by the azide displacement scheme. Alkylation as above afforded the *p*-fluorobutyrophenone **27.**

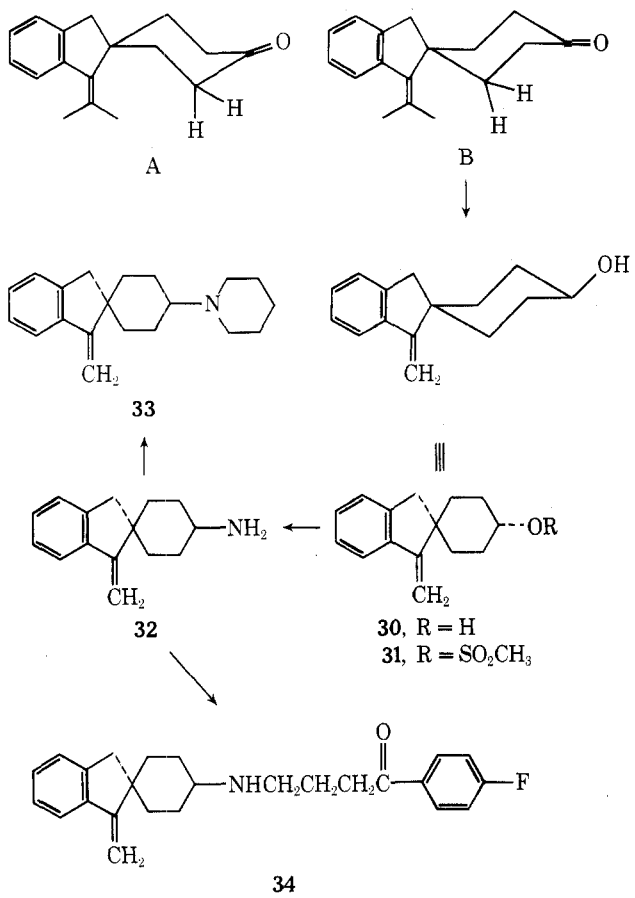



Reaction of ketone **8a** with methylmagnesium bromide proceeds uneventfully to afford the tertiary alcohol **28.** An attempt to deketalize this compound under the usual mild conditions, surprisingly resulted in dehydration of the alcohol to afford the *exo*-methylene ketone **29.** The ketone was

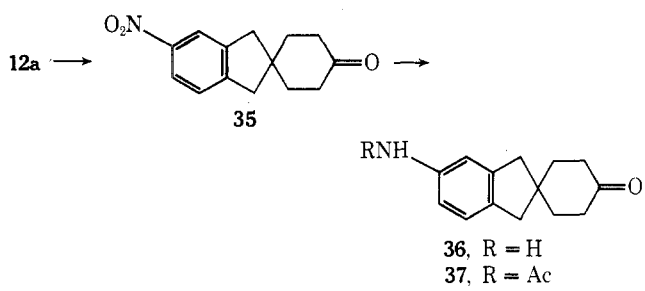



then reduced by means of sodium borohydride. Careful chromatography of the product afforded first a trace of an alcohol whose NMR spectrum was consistent with an axial hydroxyl group; the bulk of the product had an NMR consistent with an equatorial group. Examination of molecular models of the starting ketone reveals two conformations which contain a chair cyclohexane (A, B). Of these, B is perhaps slightly favored since it does not contain the interaction of the exomethylene group with the axial protons on the 3 positions on the cyclohexane. Granting this assumption, the equatorial alcohol obtained from this conformer would be formulated as in **30.** Formation of the mesylate gave **31.** This is of course inverted in the azide displacement step; the amine obtained by reduction of the azide is thus tentatively formulated as **32.** Alkylation of this last product with 1,5-diiodopentane affords the piperidine **33;** reaction with the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis gives butyrophenone **34.**

Finally, nitrogen was introduced as an attachment to the aromatic ring. Treatment of a solution of the ketone **12a** in trifluoroacetic acid in the cold with a limited amount of nitric acid gave the corresponding nitro compound in modest yield. Reduction of **35** was accomplished by catalytic hy-



drogenation. Since the free amine proved rather unstable, the compound was characterized as its acetamide (**37**).



## Experimental Section[7]

**4-Carbomethoxycyclohexanone Cyclic Ethylene Acetal (3).** A mixture of 17.41 g (0.11 mol) of 4-carbomethoxycyclohexanone,[3] 6.25 ml of ethylene glycol, and 0.25 g of *p*-toluenesulfonic acid in 200 ml of benzene was heated at reflux under a Dean-Stark trap for 5 hr. The mixture was allowed to cool, washed in turn with saturated aqueous sodium bicarbonate, water, and brine, and taken to dryness. The residual oil was distilled at 0.5 mm to afford 20.0 g (91%) of product: bp 96–100°; ir 2960, 1735, 1195, 1170, 1135, 1105, and 925 $cm^{-1}$.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.15; H, 8.45.

**4-Benzyl-4-carbomethoxy-1-cyclohexanone Cyclic Ethylene Acetal (4a).** To a solution of 5.0 g (0.05 mol) of diisopropylamine in 50 ml of THF cooled in ice–MeOH there was added over 5 min 32 ml of 1.57 *N* BuLi in pentane. There was then added in turn 10.0 g (0.05 mol) of 4-carbomethoxy-1-cyclohexanone cyclic ethylene acetal in 50 ml of THF (15 min) and 8.50 g (0.05 mol) of $\alpha$-bromotoluene in 15 ml of THF (5 min). The clear solution was stirred at room temperature for 1 hr, cooled in ice again, and treated with 50 ml of saturated $NH_4Cl$. The organic layer was separated, diluted with $C_6H_6$, and washed in turn with $H_2O$, ice-cold 1 *N* HCl, $NaHCO_3$, and brine. The oil which remained when the organic layer was taken to dryness was distilled at 0.25 mm to afford 13.57 g (93.5%) of product as a viscous oil: bp 155–156°; NMR $\delta$ 1.7 (m, 8, $CH_2$), 2.8 (s, 2, $ArCH_2$), 3.58 (s, 3, $OCH_3$), 3.93 (s, 4, ketal), 7.18 (m, 5, ArH); ir 2950, 1725, 1210, 1190, 1150, 1105, and 705 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 69.94; H, 7.60.

**4-(*m*-Methoxybenzyl)-4-carbomethoxy-1-cyclohexanone Cyclic Ethylene Acetal (4b).** The ester (19.6 g, 0.0995 mol) was alkylated as above with 15.3 g of *m*-methoxybenzyl chloride to give 22.32 g (70%) of ester acetal: bp 159–165° (0.2 mm); ir 2950, 1725, 1260, 1205, 1190, 1155, and 1105 $cm^{-1}$.

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.71; H, 7.81.

**1-Benzyl-4-cyclohexanone-1-carboxylic Acid (6a).** A mixture of 16.64 g (0.057 mol) of the ester ketal and 2.5 g of KOH in 100 ml of ethylene glycol was stirred at reflux overnight. The mixture was then allowed to cool and diluted with $H_2O$. The solution was washed once with $H_2O$ and then made strongly acidic with concentrated HCl. The precipitated gum was extracted with $Et_2O$ and this solution washed in turn with $H_2O$ and brine and taken to dryness. A solution of the residue and 13 ml of 2.5 *N* HCl in 130 ml of $Me_2CO$ was stirred at room temperature for 20 hr. The bulk of the solvent was then removed under vacuum and the residue dissolved in ether. The organic layer was washed with water and brine and taken to dryness. The residual gum was chromatographed on 800 ml of acid-washed silica gel (elution with 4% AcOH in $CH_2Cl_2$). The crystalline fractions were combined and recrystallized twice from $CH_2Cl_2$–cyclohexane. There was obtained 5.62 g (42%) of the keto acid: mp 120–123°; ir 3160, 1730, 1690, 1220, 1180, and 705 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.24; H, 6.86.

**4-(*m*-Methoxybenzyl)-1-cyclohexanone-1-carboxylic Acid (6b).** Ester ketal **4b** (24.3 g, 0.076 mol) was saponified and isolated as above. The resulting solid was recrystallized twice from $Et_2O$–Skellysolve B (SSB)[8] to give 7.8 g (36%) of the desired keto acid, mp 109–112.5°, and a second crop of 3.82 g (19%) of product: mp 109–111°; ir 3040, 1730, 1690, 1260, 1185, 1155, and 1050 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.30; H, 6.92.

**Spiro[cyclohexane-1,2′-indan]-1′,4-dione (7a).** To 100 ml of freshly distilled hydrogen fluoride there was added 14.63 g (0.063 mol) of the keto acid. The solution was allowed to stand at room temperature for 18 hr and then poured cautiously into saturated $NaHCO_3$. The precipitated gum was extracted with $C_6H_6$. The organic layer was washed with $H_2O$, $NaHCO_3$, and brine and taken to dryness. The residue was chromatographed over 1.5 l. of silica gel (elution with 20% $Me_2CO$ in SSB). There was obtained first a small amount of by-product followed by 10.50 g (78%) of spiro diketone, mp 70.5–72°. A small sample from another run was obtained as polymorph to mp 61–64°; ir 1705, 1600, 1285, and 740 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.43; H, 6.59.

The less polar by-product was recrystallized from petroleum ether to give 0.28 g of product (**10**): mp 77–78°; ir 1705, 1290, 1270, 1115, 1065, 1000, 915, and 730 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{14}F_2O$: C, 71.17; H, 5.97; mol wt, 236. Found: C, 71.18; H, 6.01; mol wt, 236.

**5′-Methoxyspiro[cyclohexane-1,2′-indan]-1′,4-dione (7b).** A suspension of 15.63 g (0.060 mol) of keto acid and 12.5 g of $PCl_5$ in 190 ml of $C_6H_5Cl$ was stirred mechanically under reflux for 1.5 hr and at room temperature for 1.5 hr. The mixture was then cooled in ice and treated with 6.85 ml of $SnCl_4$. Following 0.5 hr of stirring in the cold and 18 hr at room temperature there was added 96 ml of 2.5 *N* HCl over 10 min. Following an additional 1 hr of stirring, the organic layer was separated, washed with $H_2O$, $NaHCO_3$, and brine, and taken to dryness. The residue was chromatographed on 1.2 l. of silica gel (elution with 10% EtOAc in $CH_2Cl_2$). The crystalline fractions were combined to give 7.51 g (51%) of product: mp 105–107°; ir 1710, 1685, 1600, 1275, 1250, and 1095 $cm^{-1}$.

The analytical sample melted at 110–112°.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; mol wt, 244. Found: C, 73.75; H, 6.65; mol wt, 244.

**Spiro[cyclohexane-1,2′-indan]-1′,4-dione Cyclic 4-(Ethylene Acetal) (8a).** A mixture of 1.77 g (0.0083 mol) of the diketone, 0.51 g (0.46 ml, 0.0082 mol) of ethylene glycol, and 0.10 g of *p*-TSA in 50 ml of $C_6H_6$ was heated at reflux under a Dean-Stark trap for 4 hr. The mixture was allowed to cool, washed in turn with $NaHCO_3$, $H_2O$, and brine, and taken to dryness. The residual solid was recrystallized from cyclohexane to afford 1.67 g (75%) of monoacetal: mp 158–160.5°; NMR $\delta$ 1.90 (m, 8, $CH_2$), 3.05 (s, 2,

$ArCH_2$), 4.0 (s, 4, ketal) 7.5 (m, 4, ArH); ir 1700, 1295, 1115, 1075, 935, 890, and 735 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02; mol wt, 258. Found: C, 73.99; H, 6.98; mol wt, 258.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-1',4-dione Cyclic 4-(Ethylene Acetal) (8b).** The diketone (4.89 g, 0.0196 mol) was ketalized as above to yield 4.13 g (73%) of monoacetal: mp 142–144°; ir 1695, 1600, 1280, 1255, 1100, and 1080 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.06; H, 7.19.

**Spiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (9a).** A mixture of 5.0 g (0.0194 mol) of the ketone, 2.6 ml of $N_2H_4 \cdot H_2O$, and 3.76 g of KOH in 50 ml of ethylene glycol was heated at reflux for 1.5 hr. Material was then removed by distillation to bring the pot temperature to 200°. At the end of an additional 5 hr heating at reflux, the mixture was allowed to cool and diluted with $H_2O$. The precipitated solid was collected on a filter, dried, and recrystallized from petroleum ether. There was obtained 4.00 g (85%) of reduced product: mp 70–74°; ir 1100, 1065, 1040, 755, and 735 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.39; H, 8.19.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (9b) and 5'-Hydroxyspiro[cyclohexane-1,2'-indan]-1',4-dione Cyclic 4-(Ethylene Acetal) 1'-Hydrazone (11).** A mixture of 4.57 g (0.0158 mol) of ketone, 2.45 g of $N_2H_4 \cdot H_2O$, and 3.15 g of KOH in 40 ml of ethylene glycol was heated at reflux for 1 hr. Solvent was removed by distillation to bring the reaction mixture to 200°. Following 1.5 hr at this temperature the mixture was poured into $H_2O$, and this was extracted well with $Et_2O$. The organic fractions were combined and taken to dryness. The residue was chromatographed on 250 ml of silica gel (elution with 10% $Me_2CO$ in SSB). There was obtained 2.07 g (48%) of product, mp 59–61°. The analytical sample from an earlier run melted at 65–66.5°: ir 1495, 1265, 1100, 1030, and 820 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.22; H, 8.08. Found: C, 74.57; H, 8.24.

The aqueous portion above was "acidified" with solid $CO_2$. The precipitated solid was collected on a filter and recrystallized from MeOH. There was obtained 0.51 g of by-product: mp 243–246°, 285–290°; ir 3340, 1605, 1595, and 1275 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.69; H, 6.99; N, 9.71; mol wt, 288. Found: C, 66.16; H, 7.14; N, 9.96; mol wt, 288.

**Spiro[cyclohexane-1,2'-indan]-4-ol (13a).** A mixture of 4.0 g (0.016 mol) of acetal and 8 ml of 2.5 *N* HCl in 80 ml of $Me_2CO$ was heated at reflux for 4 hr. The bulk of the solvent was removed under vacuum and $Et_2O$ was added. The organic layer was separated, washed with $H_2O$ and brine, and taken to dryness. The residue was chromatographed on 350 ml of silica gel (elution with $CH_2Cl_2$). Those fractions similar by TLC were combined to afford the ketone as an amorphous gum: NMR $\delta$ 2.18 ($A_2B_2$, 8, $CH_2$), 2.95 (s, 4, $ArCH_2$), 7.18 (s, 4, ArH).

To a solution of 8.33 g (0.042 mol) of the crude oily ketone in 85 ml of EtOH there was added 1.60 g of $NaBH_4$. Following 6 hr stirring at room temperature the bulk of the solvent was removed under vacuum. The residue was taken up in $Et_2O$ and $H_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was chromatographed on 800 ml of silica gel (elution with 1% $Me_2CO$ in $CH_2Cl_2$). The crystalline fractions were combined and recrystallized from petroleum ether to give 5.52 g (66%) of product: mp 76–78°; ir 3270, 1080, 1050, and 735 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.33; H, 8.92.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-ol (13b).** The acetal (2.87 g, 0.0105 mol) was hydrolyzed as above to give 1.95 g (81%) of ketone: mp 89–91°; ir 1715, 1495, 1290, 1245, and 1030 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.96; H, 7.96.

This was reduced ($NaBH_4$) to give the alcohol as an oil.

**Spiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (14a).** A mixture of 5.52 g (0.027 mol) of the alcohol in 50 ml of ice-cold pyridine was treated with 5.5 ml of $CH_3SO_2Cl$. Following 7 hr standing in the cold the mixture was diluted with ice–$H_2O$. The precipitated solid was recrystallized from $Me_2CO$–SSB to give 7.15 g (93%) of mesylate: mp 100–102°; ir 1355, 1345, 1340, 1330, 1185, 1160, 920, and 905 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.87; H, 7.50.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (14b).** The alcohol (1.86 g, 0.0080 mol) was acylated as above to give 2.10 g (85%) of mesylate: mp 63–67; ir 1490, 1350, 1245, 1170, 950, and 855 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.80; H, 7.14.

**Spiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (15a).** A mixture of 7.15 g (0.0256 mol) of the mesylate and 7.0 g of sodium azide in 70 ml of DMF was stirred in an oil bath at 90° for 17 hr. The solvent was then removed under vacuum and the residue dissolved in $C_6H_6$ and $H_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness.

A solution of the crude azide in 75 ml of THF was added to a well-stirred suspension of 1.0 g of $LiAlH_4$ in 25 ml of THF. Following 5 hr of stirring at room temperature, the mixture was cooled in ice and treated in turn with 1 ml of $H_2O$, 1 ml of 15% NaOH, and 3 ml of $H_2O$. The inorganic gel was removed by filtration and the filtrate taken to dryness. The residue was dissolved in $Et_2O$ and this treated with 5 *N* HCl in $Et_2O$. The precipitated solid was recrystallized from MeOH–EtOAc to give 4.58 g (76%) of amine: mp 280–282°; ir 3000, 1500, 1485, 755, and 740 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.71; H, 8.48; N, 5.89. Found: C, 70.68; H, 8.55; N, 5.69.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (15b).** The mesylate (2.10 g, 0.0068 mol) was converted to the azide and this reduced as above to give 0.69 g (38%) of product: mp 274–277°; ir 3130, 1580, 1495, 1290, 1250, and 1035 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.25; H, 8.18; N, 4.98.

Concentration of the mother liquors afforded 0.43 g (23%) of an apparently polymorphic form of the product, mp 246–248°.

Anal. Found: C, 66.98; H, 8.50; N, 4.87; *m/e* 231.

**4'-Fluoro-4-(spiro[cyclohexane-1,2'-indan]-4-yl)amine Butyrophenone Hydrochloride (18a).** To a solution of 1.12 g (0.0047 mol) of the amine hydrochloride in 30 ml of DMF there was added 0.22 g of NaH. Following 1 hr of stirring at room temperature there was added 0.81 g of KI, 1.32 g of $K_2CO_3$, and 1.14 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal. The mixture was then stirred overnight in an oil bath at 90°. The solvent was removed under vacuum and the residue dissolved in $C_6H_6$ and $H_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was then stirred with 15 ml of MeOH and 7.5 ml of 2.5 *N* HCl for 2 hr. The bulk of the MeOH was removed under vacuum and the solid collected on a filter. Two recrystallizations from $CH_2Cl_2$–EtOAc afforded 0.84 g (46%) of product: mp 195–198°; ir 2760, 2500, 1680, 1595, 1155, 835, and 770 $cm^{-1}$.

Anal. Calcd for $C_{24}H_{29}ClFNO$: C, 71.71; H, 7.27. Found: C, 71.68; H, 7.14.

**4'-Fluoro-4-[5'-methoxyspiro[cyclohexane-1,2'-indan]-4-yl)aminobutyrophenone Hydrochloride (18b).** The amine hydrochloride (0.69 g, 0.0026 mol) was alkylated and the product isolated as above to give 0.52 g (46%) of product: mp 190–193°; ir 2760, 1680, 1600, 1495, 1290, 1275, and 1240 $cm^{-1}$.

Anal. Calcd for $C_{25}H_{31}ClFNO_2$: C, 69.51; H, 7.23; N, 3.24. Found: C, 69.62; H, 7.20; N, 3.11.

**Spiro[cyclohexane-1,2'-indan]-4-methylamine Hydrochloride (17a).** A suspension of 3.03 g (0.0128 mol) of the salt in $CH_2Cl_2$ was shaken with 1 *N* NaOH until the solid had all dissolved. The organic layer was separated and taken to dryness. To an ice-cooled solution of the residue in 25 ml of pyridine there was added dropwise 2 ml of $ClCO_2C_2H_5$. At the end of 5 hr in the cold the mixture was poured onto ice–$H_2O$. The precipitated solid was recrystallized from SSB to give 2.90 g (83%) of carbamate, mp 70–73°.

A solution of 2.90 g (0.0106 mol) of the carbamate in 50 ml of THF was added to a well-stirred suspension of 0.50 g of $LiAlH_4$ in 25 ml of THF. The mixture was heated at reflux for 6 hr and then cooled in ice. There was added in turn 0.5 ml of $H_2O$, 0.5 ml of 15% NaOH, and 1.5 ml of $H_2O$. The inorganic gel was collected on a filter and the filtrate taken to dryness. A solution of the residue in $Et_2O$ was treated with 6 *N* HCl in $Et_2O$. The precipitate was recrystallized from $CH_2Cl_2$–MeOH–EtOAc to give 1.80 g (66%) of product, mp 251–254°.

Anal. Calcd for $C_{15}H_{22}ClN \cdot \frac{1}{3}H_2O$: C, 69.88; H, 9.22; N, 5.43. Found: C, 69.99; H, 8.55; N, 5.25.

**5'-Methoxyspiro[cyclohexane-1,2'-indan]-4-methylamine Hydrochloride (17b).** Reduction of the waxy carbamate, prepared as above, afforded on work-up a 35.1% yield of the secondary amine hydrochloride, mp 225–229°.

Anal. Calcd for $C_{16}H_{24}ClNO \cdot \frac{1}{2}CH_3OH$: C, 66.53; H, 8.80; N, 4.70. Found: C, 66.74; H, 8.54; N, 4.82.

**4'-Fluoro-4-[methyl(spiro[cyclohexane-1,2'-indan]-4-yl)-amino]butyrophenone Hydrochloride (19a).** Alkylation of the secondary amine (1.0 g, 0.0040 mol) with the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis and work-up afforded 0.77 g (45%) of product: mp 195–197°; ir 2450, 1675, 1595, 1225, 1150, 830, and 730 $cm^{-1}$.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 70.65; H, 7.35; N, 3.29. Found: C, 71.10; H, 7.44; N, 3.20.

**4'-Fluoro-4-[methyl(5'-methoxyspiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone, Hydrochloride (19b).** Proceeding exactly as above, alkylation of the amine (0.84 g, 3.0 mmol) with 4-chloro-*p*-fluorobutyrophenone-2,2-dimethylpropylene acetal followed by hydrolysis afforded 0.45 g (33.6%) of the butyrophenone as an amorphous foam.

**1-Spiro[cyclohexane-1,2'-indan]-4-yl Piperidine Hydrochloride (20).** To a suspension of 1.53 g (0.0065 mol) of the amine hydrochloride in 30 ml of EtOH there was added 1.58 ml of 4.2 *N* NaOMe in MeOH. Following 1 hr of stirring 1.62 g of $K_2CO_3$ and 0.97 ml of 1,5-diiodopentane were added and the mixture brought to reflux. At the end of 18 hr the mixture was allowed to cool and the bulk of the solvent removed under vacuum. The residue was partitioned between $Et_2O$ and $H_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residual solid was dissolved in $Et_2O$ and this treated with 5 *N* HCl in $Et_2O$. The resulting precipitate was recrystallized from $CH_2Cl_2$–EtOAc to afford 1.53 g (77%) of product: mp 282–286°; ir 2620, 2520, 1038, 755, and 730 $cm^{-1}$.

Anal. Calcd for $C_{19}H_{28}ClN$: C, 74.60; H, 9.23; N, 4.58. Found: C, 74.33; H, 9.27; N, 4.71.

**1'-Hydroxyspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (21).** A solution of 2.60 g (0.010 mol) of the ketone in 50 ml of THF was added to a well-stirred suspension of 0.50 g of $LiAlH_4$ in 10 ml of THF. The mixture was stirred at room temperature for 5 hr, cooled in ice, and treated in turn with 0.5 ml of $H_2O$, 0.5 ml of 15% NaOH, and 1.5 ml of $H_2O$. The inorganic gel was removed by filtration and the filtrate taken to dryness. The residue was recrystallized from cyclohexane to give 2.45 g (95%) of product: mp 125–128°; ir 3450, 1090, 1035, 1025, 755, and 725 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.48; H, 7.78.

**1'-Acetoxy(cyclohexane-1,2'-indan)-4-one (23).** A solution of 2.45 g (0.0094 mol) of the ketal and 5 ml of 2.5 *N* HCl in 50 ml of $Me_2CO$ was allowed to stand overnight at room temperature. The bulk of the solvent was then removed under vacuum and the residue dissolved in $H_2O$ and $Et_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness to afford the product as a gum, $\nu_{max}$ 3500, 1705 $cm^{-1}$.

A solution of the gum and 4 ml of $Ac_2O$ in 16 ml of pyridine was allowed to stand at room temperature for 7 hr and then poured onto ice–$H_2O$. The precipitate was extracted with $Et_2O$. This extract was washed in turn with $H_2O$, ice-cold 2.5 *N* HCl, $H_2O$, and saturated $NaHCO_3$ and taken to dryness. The residual solid was recrystallized from SSB to give 1.82 g (75%) of acetoxy ketone: mp 87–89°; NMR $\delta$ 2.05 (s, 3, $COCH_3$), 2.10 (m, 9), 3.0 (s, 2, ArCH), 3.10 (s, 1, ArCH), 7.25 (s, 4, ArH); ir 1725, 1240, 1210, 1020, 975, 770, and 755 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 73.99; H, 6.95.

**1'-Acetoxy(cyclohexane-1,2'-indan)-4-ol Methanesulfonate (25).** To a solution of 1.82 g (0.0071 mol) of acetoxy ketone in 25 ml of 95% *i*-PrOH there was added 0.32 g of $NaBH_4$. Following 1 hr stirring at room temperature the bulk of the solvent was removed under vacuum. The residue was dissolved in $Et_2O$ and $H_2O$; the organic layer was washed with $H_2O$ and brine and taken to dryness.

The residual gum was dissolved in 15 ml of pyridine. This solution was cooled in ice and treated with 1.7 ml of $CH_3SO_2Cl$. Following 17 hr of standing in the cold the mixture was poured onto ice–$H_2O$. The precipitated gum was extracted with $Et_2O$. The organic layer was washed in turn with $H_2O$, 2.5 *N* HCl, $H_2O$, and brine and taken to dryness. The residue was recrystallized twice from $Et_2O$–petroleum ether to give 1.54 g (65%) of mesylate: mp 97–100°; ir 1725, 1350, 1345, 1245, 1180, 1170, and 905 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.69; H, 5.99; mol wt, 338. Found: C, 60.60; H, 6.58; mol wt, 338.

**1'-Hydroxyspiro[cyclohexane-1,2'-indan]-4-amine (26).** The mesylate (5.0 g, 0.015 mol) was converted to the azide and this reduced ($LiAlH_4$) exactly as above. The product was recrystallized from a small amount of EtOAc to afford 1.71 g (53%) of amino alcohol, mp 156–160°; the analytical sample melted at 158–161°.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 76.98; H, 8.79; N, 6.41. Ir 3340, 3270, 2710, 1600, 1035, 770, 750, and 720 $cm^{-1}$.

**4'-Fluoro-4-[(1'-hydroxyspiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone Hydrochloride.** The amino alcohol (1.71 g, 0.0079 mol) was alkylated with the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone as above. There was obtained 1.03 g (33%) of product, mp 190–193°.

Anal. Calcd for $C_{24}H_{29}ClFNO_2$: C, 68.97; H, 6.99; N, 3.35. Found: C, 69.37; H, 7.77; H, 3.11.

**1'-Hydroxy-1'-methylspiro[cyclohexane-1,2'-indan]-4-one Cyclic Ethylene Acetal (28).** A solution of 5.0 g (0.019 mol) of the ketone in 60 ml of THF was added to 67 ml of 3 *M* $CH_3MgBr$ in $Et_2O$. Following 17 hr standing at room temperature, the mixture was cooled in ice and treated cautiously with 50 ml of saturated $NH_4Cl$. The organic layer was separated, diluted with $C_6H_6$, and washed in turn with $H_2O$ and brine. The solid which remained when the solution was taken to dryness was recrystallized from $CH_2Cl_2$–cyclohexane to give 3.70 g (71%) of product: mp 140–143°; NMR $\delta$ 1.48 (s, 3, $CH_3$), 1.78 (m, 8, $CH_2$), 2.95 (d, 2, $ArCH_2$), 4.0 (s, 4, ketal), 7.4 (m, 4, ArH); ir 3490, 1215, 1115, 1095, and 775 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.47; H, 8.08. Found: C, 74.21; H, 8.09.

**1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-one (29).** A solution of 9.82 g (0.036 mol) of the acetal and 25 ml of 2.5 *N* HCl in 250 ml of $Me_2CO$ was stirred at room temperature overnight. The solvent was then removed under vacuum and the residue dissolved in $Et_2O$ and $H_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was recrystallized from petroleum ether to give 5.12 g (67%) of solid: mp 60–62°; NMR $\delta$ 2.18 ($A_2B_2$, 8, $CH_2$), 3.17 (s, 2, $ArCH_2$), 4.88 (s, 1, vinyl), 5.42 (s, 1, vinyl), 7.28 (m, 4, ArH).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.46; H, 7.97.

**1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-3-ol (30).** A mixture of 2.17 g (0.010 mol) of the ketone and 0.75 g of $NaBH_4$ in 40 ml of *i*-PrOH was stirred at room temperature for 6 hr. The solvent was removed under vacuum and the residue dissolved in $H_2O$ and $Et_2O$. The organic layer was washed with $H_2O$ and brine and taken to dryness. The residue was chromatographed on 250 ml of silica gel (elution with 20% $Me_2CO$–SSB). There was obtained first 0.08 g of solid: mp 65–69°; NMR $\delta$ 1.84 (m, 8, $CH_2$), 2.90 (s, 2, $ArCH_2$), 4.10 (m, $W_{1/2}$ = 10 Hz, 1, CHOH), 5.10 (s, 1, vinyl), 5.50 (s, 1, vinyl), 7.28 (m, 4, ArH). This was followed by a gum which crystallized only in the presence of $H_2O$: 1.71 g (78%); mp 57–61°; NMR $\delta$ 1.72 (m, 8, $CH_2$), 2.90 (s, 2, $ArCH_2$), 3.70 (m, $W_{1/2}$ = 20 Hz, 1, CHOH), 4.92 (s, 1, vinyl), 5.50 (s, 1, vinyl), 7.22 (m, 4, ArH). No satisfactory analysis could be obtained for this material.

**1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-ol Methanesulfonate (31).** The major alcohol (4.26 g, 0.020 mol) was converted to the mesylate in the usual way. There was obtained 4.82 g (83%) of solid: mp 72–74°; ir 1350, 1335, 1175, 970, 935, 870, and 790 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; mol wt, 292. Found: C, 65.32; H, 7.12; mol wt, 292.

**1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]-4-amine Hydrochloride (32).** The mesylate (5.65 g, 0.019 mol) was taken on to the amine via the azide as above. There was obtained 3.08 g (61%) of product: mp 250–253°; ir 3000, 1640, 1600, 1510, 875, 775, 735, and 720 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{20}ClN \cdot H_2O$: C, 67.29; H, 8.28; N, 5.23. Found: C, 67.50; H, 7.92; H, 5.21.

**1'-*exo*-Methylenespiro[cyclohexane-1,2'-indan]piperidine (33).** The amine prepared from 1.41 g (0.0056 mol) of the hydrochloride, 1.81 g of 1,5-diiodopentane, and 1.55 g of $K_2CO_3$ in 15 ml of EtOH was stirred at reflux for 18 hr. The mixture was allowed to cool and diluted with water and the solid was collected on a filter. This was recrystallized from MeOH to give 1.05 g (67%) of solid: mp 93–95°; ir 1630, 985, 865, 775, and 730 $cm^{-1}$.

Anal. Calcd for $C_{20}H_{27}N$: C, 85.35; H, 9.67; N, 4.90. Found: C, 85.58; H, 9.99; N, 5.24.

**4'-Fluoro-4-[(1'-methylenespiro[cyclohexane-1,2'-indan]-4-yl)amino]butyrophenone Hydrochloride (34).** The amine hydrochloride (2.0 g, 0.0080 mol) was converted to the butyrophenone as above. There was obtained 0.95 g (29%) of product: mp 208–211°; ir 2780, 1680, 1600, 1230, and 735 $cm^{-1}$.

Anal. Calcd for $C_{25}H_{29}ClFNO$: C, 72.53; H, 7.06; N, 3.38. Found: C, 72.20; H, 7.19; N, 3.68.

**3'-Nitrospiro[cyclohexane-1,2'-indan]-4-one (35).** To an ice-

cooled solution of 9.04 g (0.045 mol) of the ketone in 45 ml of TFA there was added 9 ml of $HNO_3$. At the end of 2 hr reaction in the cold, the solution was poured onto ice–$H_2O$. The precipitated solid was chromatographed on 1 l. of silica gel (elution with 25% $Me_2CO$–SSB). The crystalline fractions were combined and recrystallized from $Me_2CO$–SSB. There was obtained 7.23 g (65%) of product, mp 124–128°. The analytical sample melted at 126–127.5°; ir 1710, 1515, 1345, 1330, 825, and 740 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.38; H, 6.24; N, 5.95.

**3′-Acetamidospiro[cyclohexane-1,2′-indan]-4-one (37).** A suspension of 0.50 g of 10% Pd/C in a solution of 7.89 g (0.032 mol) of nitro ketone in 150 ml of EtOAc was shaken under $H_2$. At the end of 3 hr an additional 0.50 g of catalyst was added and shaking resumed. When the theoretical uptake had been observed the catalyst was removed by filtration and a solution of 6.1 g of *p*-TSA in a small amount of MeOH added. The solvent was removed under vacuum and an attempt made to recrystallize the residue from MeOH–$Me_2CO$. On standing in the cold over the weekend extensive decomposition occurred. The material was then reconverted to the free base. A solution of this in 40 ml of pyridine was treated with 10 ml of $Ac_2O$. At the end of 5 hr the mixture was poured onto ice–$H_2O$. The precipitate was extracted with $CH_2Cl_2$. This solution was washed with $H_2O$, 2.5 *N* HCl, $H_2O$, and brine and taken to dryness. The residue was chromatographed on 700 ml of silica gel (elution with 25% $Me_2CO$–$CH_2Cl_2$). The crystalline fractions were combined and recrystallized from MeOH. There was obtained 3.15 g (38%) of product: mp 169–171°; ir 3340, 1695, 1680, 1600, 1540, 1490, and 1290 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; mol wt, 257. Found: C, 74.36; H, 7.54; N, 5.48; mol wt, 257.

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**Registry No.**—**3,** 26845-47-6; **4a,** 56868-10-1; **4b,** 56868-11-2; **6a,** 56868-12-3; **6b,** 56868-13-4; **7a,** 56868-14-5; **7b,** 56868-15-6; **8a,** 56908-37-3; **8b,** 56868-16-7; **9a,** 56868-17-8; **9b,** 56868-18-9; **10,** 56868-19-0; **11,** 56868-20-3; **12a,** 56868-21-4; **12b,** 56868-22-5; **13a,** 56868-23-6; **13b,** 56868-24-7; **14a,** 56868-25-8; **14b,** 56868-26-9; **15a,** 56868-27-0; **15b,** 56858-28-1; **16a,** 56868-29-2; **16b,** 56868-30-5; **17a,** 56868-31-6; **17b,** 56908-38-4; **18a,** 56868-32-7; **18b,** 56868-33-8; **19a,** 56868-34-9; **19b,** 56868-35-0; **20,** 56868-37-2; **21,** 56868-38-3; **23,** 56868-39-4; **25,** 56868-40-7; **26,** 56868-41-8; **27,** 56868-42-9; **28,** 56868-43-0; **29,** 56868-44-1; **30,** 56868-45-2; **31,** 56868-46-3; **32,** 56868-47-4; **33,** 56868-48-5; **34,** 56868-36-1; **35,** 56868-49-6; **37,** 56868-50-9; 4-carbomethoxycyclohexanone, 6297-22-9; ethylene glycol, 107-21-1; *m*-methoxybenzyl chloride, 824-98-6; 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal, 36714-65-5; carbonochloridic acid ethyl ester, 541-41-3.

## References and Notes

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(4) See, for example, J. J. Eisch, *J. Org. Chem.*, **28,** 707 (1962).
(5) P. A. J. Janssen, C. J. E. Niemegeers, and K. L. H. Schellekens, *Arzneim.-Forsch.*, **15,** 104 (1965).
(6) Applying the same argument as in the case of the *exo*-methylene compound **29** would suggest that the two oxygen atoms in **24** occupy an anti relationship.
(7) All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. NMR spectra were determined in deuteriochloroform on a Varian A-60D NMR spectrometer. Infrared spectra were obtained on either a Perkin-Elmer Model 421 or on a Digilab Model 14D spectrophotometer. Solids were prepared as mineral oil mulls while liquids were prepared neat between sodium chloride plates. Mass spectra were obtained with an Atlas MAT CH4 instrument. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental analyses.
(8) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

# Benzospirans Bearing Basic Substitution. II. Amines Derived from 3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-one and 3′,4′-Dihydro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one

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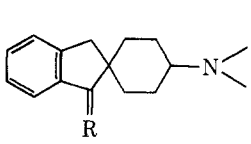
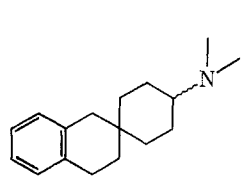
The cyclic ethylene acetal of 4-benzyl-4-carbethoxycyclohexan-1-one was homologated to the corresponding acetic acid via the nitrile. Removal of the acetal followed by cyclization gave spiro[cyclohexane-1,2′(1′*H*)-naphthalene]-4,4′(3′*H*)-dione. Taking advantage of the differing reactivities of the two carbonyl groups that compound was converted in several steps to 3′,4′-dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-one. The two isomeric amines were prepared from the ketone. The configuration of these products was assigned the basis of NMR. Double homologation via Wittig reaction on 4-oxo-1-phenylcyclohexanecarboxaldehyde 4-cyclic ethylene acetal followed by reduction gave the corresponding propionic acid. This was taken in a series of steps analogous to those above to 3′,4′-dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one. The ketone was converted to the corresponding amine via the mesylate. The configuration of these amines is discussed as well.

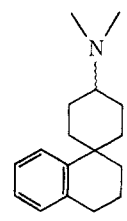
The subtle stereochemical effects observed in the course of the preparation of the spirocyclohexylindans (**1**),[1] particularly when those compounds bore substitution on the benzylic carbon (**2**), encouraged us to examine the corresponding spirocyclohexyltetralins (**3, 4**).



1, R, $H_2$
2, R, $CH_2$; R, H, OH



3



4

**Derivatives of 3′,4′-Dihydrospiro[cyclohexane-1,-2′(1′*H*)naphthalen]-4-one.** Preparation of the spiran containing the cyclohexyl group attached to the 2 position of the tetralin **3** is rendered easier by the fact that this carbon skeleton differs from that of **1**, which we had prepared earlier, only by the interposition of a methylene group. The first task thus consisted in the preparation of a homologue of the acid used to prepare the spiro indan (Scheme I). Reduction of the ester **5** used as source of the carbon skeleton in the earlier work by means of lithium aluminum hydride smoothly gave the corresponding alcohol **6**; this was converted to its methanesulfonate by conventional means. Initial attempts to effect displacement of the mesylate with cyanide ion under a variety of conditions bore evidence for