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.

Acknowledgment. The authors are indebted to Mr. Paul A. Meulman of The Upjohn Co. for obtaining and interpreting the infrared spectral data.

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

(1) D. Lednicer, D. E. Emmert, R. Lahti, and A. D. Rudzik, *J. Med. Chem.*, **15**, 1235 (1972).

(2) D. Lednicer, D. E. Emmert, R. Lahti, and A. D. Rudzik, *J. Med. Chem.*, **15**, 1239 (1972).

(3) S. Siegel and J. M. Komarmy, *J. Am. Chem. Soc.*, **82**, 2547 (1960).

(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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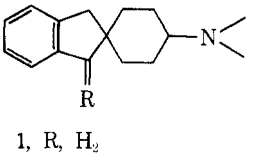
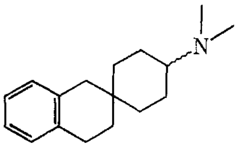
Received May 8, 1975

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



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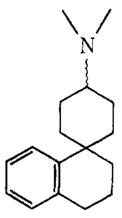
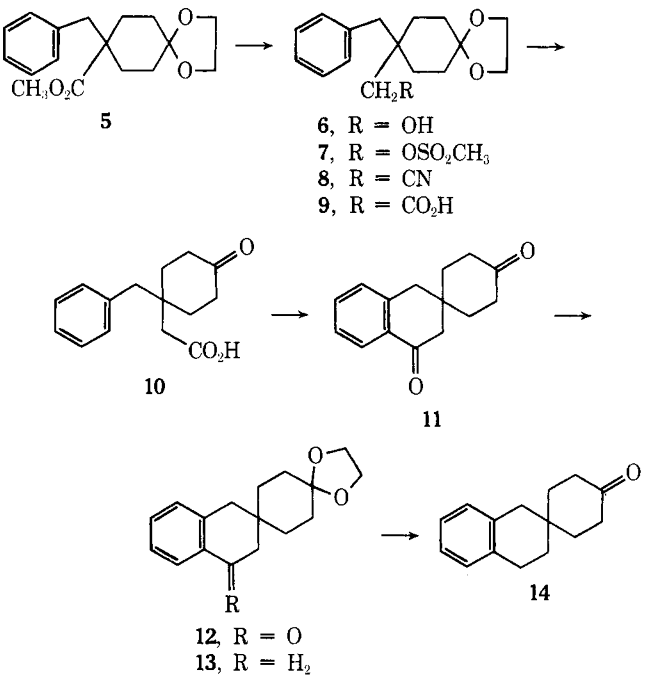


4

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

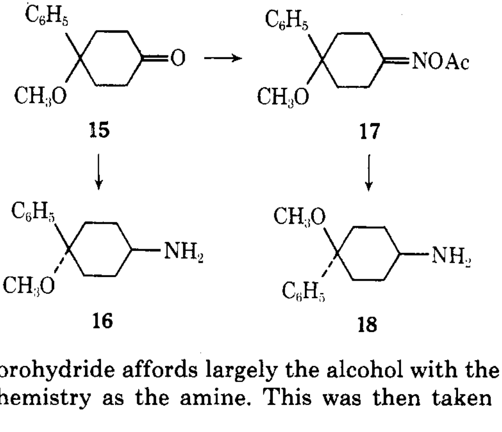
Scheme I



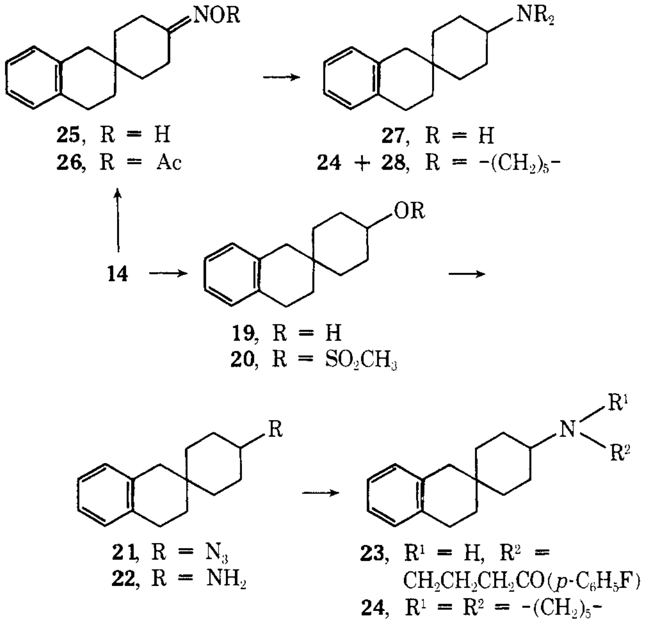
the highly hindered milieu of the reaction site. Starting material was thus recovered unchanged from treatment of 7 with potassium cyanide in DMF at 140°C. Simple substitution of hexamethylphosphoric triamide (HMPA) for DMF in this last reaction unexpectedly resulted in complete disappearance of starting material with the appearance of a single product. The oily nitrile 8 was isolated by chromatography; this material was saponified to the acid 9 without further characterization (potassium hydroxide in ethylene glycol). The high overall yield for the conversion of mesylate to acid (77%) attests to the efficacy of HMPA as solvent in this displacement. Removal of the ketal affords the desired homologated keto acid 10.

Cyclization to the spiro diketone 11 was effected in workable yield by means of liquid hydrogen fluoride. The product was then converted to the monoketone 14 by first selective protection of the cyclohexanone as its ethylene ketal; reduction of the aromatic ketone by Wolff–Kishner reaction followed by deketalization afforded the desired product as an oil.

In earlier work on the preparation of cyclohexylamines containing geminal substituents at the 4 position we had developed stereoselective schemes for the preparation of the isomeric compounds.[2] Thus, conversion of cyclohexanone 15 to its oxime acetate followed by reduction with diborane afforded the isomer containing the cis amine and ether groups (18). Reduction of the ketone by means of sodium borohydride affords largely the alcohol with the same stereochemistry as the amine. This was then taken on to the epimeric amine 16 by conversion to the mesylate, inversion by displacement with azide, and finally reduction.



Scheme II

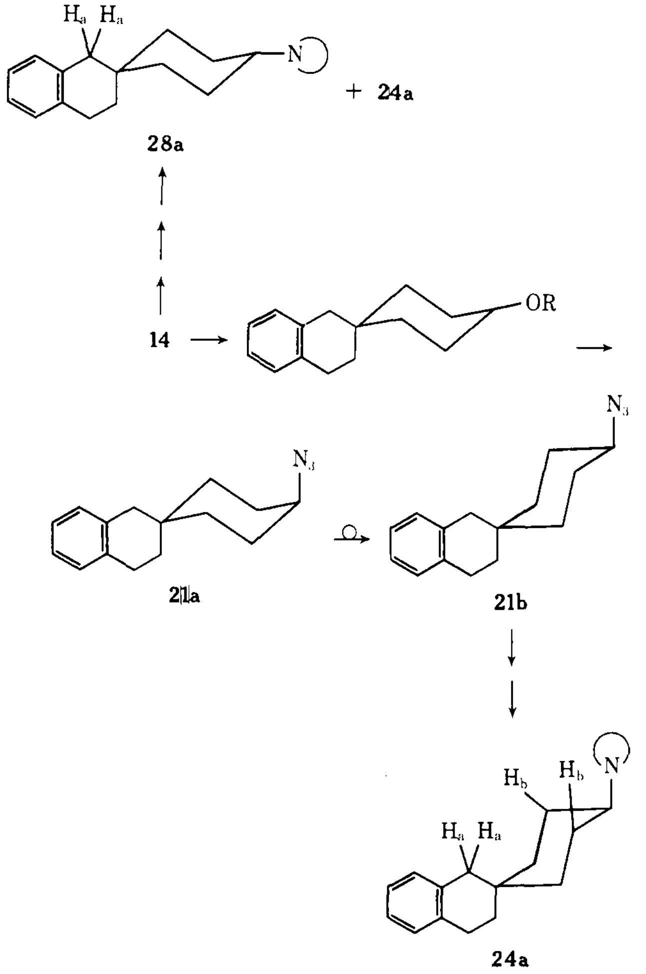


We thus anticipated that application of analogous schemes to ketone 14 would lead to the isomeric amines (Scheme II). Treatment of the spiro ketone with sodium borohydride followed by chromatography of the product afforded alcohol 19 as a crystalline solid. The NMR spectrum of this product showed the carbinyl proton as a broad band ($W_{1/2}$ = 15 Hz) centered at δ 3.55, suggestive of an equatorial hydroxyl group. This assignment must remain tentative in view of our failure to isolate any of the axial isomer for purpose of comparison. The mesylate 20 showed a similar signal in the NMR though now displaced to δ 4.7. Contrary to our expectations, the corresponding proton in the azide 21, obtained by treatment of the mesylate with sodium azide, also seemed to have the equatorial configuration. The 100-MHz NMR spectrum of that compound resolved that band (δ 3.25) into a seven-line pattern characteristic of axial protons on cyclohexanes.[3] Setting this puzzle aside for the moment, the azide was reduced to the corresponding amine 22 by means of lithium aluminum hydride. Alkylation by means of the neopentyl glycol ketal of 4-chloro-*p*-fluorobutyrophenone followed by hydrolysis afforded the derivative 23. Treatment of the primary amine with 1,5-diiodopentane afforded the corresponding piperidine 24, mp 293°C; the 100-MHz NMR spectrum of this last again shows a signal for the proton on carbon bearing nitrogen (δ 2.25) with a multiplicity suggesting an axial hydrogen.

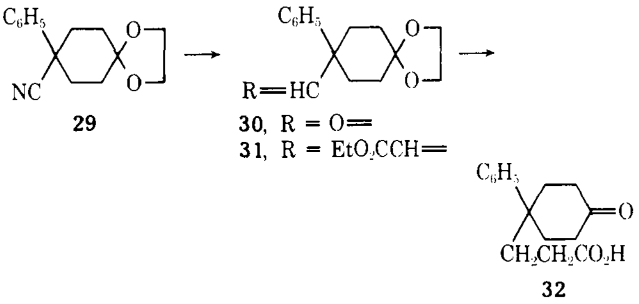
In the scheme intended to obtain the isomeric amine, the ketone 14 was converted to its oxime (25) in high yield. Acetylation (26) followed by reduction of the total crude acetate by means of diborane in THF afforded on work-up a modest yield of a mixture of isomeric amines which resisted attempts at separation by conventional means. This mixture was thus converted to the corresponding piperidines by alkylation with 1,5-diiodopentane. Fractional crystallization of the hydrochloride salt afforded first a compound which proved identical with the piperidine, mp 293°C, obtained by the azide route (24). There was obtained in addition a second piperidine, mp 263°C, whose 100-MHz spectrum also showed a signal (δ 2.25) with multiplicity suggestive of an equatorial piperidine group.

More detailed examination of the 100-MHz NMR spectra of the isomeric piperidines shows the signal for protons on the one carbon benzyl bridge (H_a) in the high-melting isomer to occur as a singlet at δ 2.62; the signal for the corresponding protons in the low-melting isomer is observed as a singlet at δ 2.46. An examination of Dreiding models reveals that there exist two isomeric amines for the gross structure (**24**, **28**) each of which carries the piperidine group in the equatorial position. Structure **24a** shows significant interaction between H_a and the axial protons on the 3 position of the cyclohexane (H_b); **28a** is free of this interaction. It has been recently shown that such steric compression is often expressed in a downfield shift for the signal of the affected protons.[4] On this basis it is thus possible to assign structure **24a** to that isomer which shows the lower field benzyl signal. Some confirmation for this assignment comes from the observation that H_a of **24** shows a barely significant downfield shift (0.05 ppm) displacement on treatment with Eu(thd)$_3$; the isomer **28** shows no effect whatever.

We rationalize these findings by the assumption that both the alcohol **19** and the mesylate **20** can be represented as equatorial isomers derived from the apparently preferred conformer of the spiran. Displacement by azide does indeed initially afford the inverted axial isomer **21a**; this then apparently undergoes a flip to the equatorial isomer **21b**. The remaining steps to **24a** do not affect the stereochemical outcome. Diborane reduction of the oxime acetate apparently affords both axial and equatorial isomers of the amine. The former can by a simple flip go to the amine **22**; the equatorial isomer goes on unchanged to the amine which affords finally the low-melting piperidine hydrochloride. No ready explanation occurs for the lack of stereoselectivity for the diborane reduction.[5]



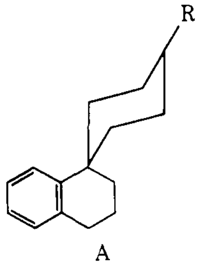
Scheme III



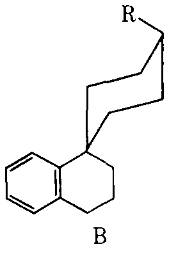
Derivatives of 3′,4′-Dihydrospiro[cyclohexane-1,-1′(2*H*′)-naphthalen]-4-one. The route chosen for the preparation of the remaining spirotetralincyclohexanone is conceptually quite similar to that described above. We required, however, a keto acid in which, at least in principle, a methylene group was transferred from the benzylic position to the acid side chain (Scheme III). Though announced quite some time ago,[6] the partial reduction of nitriles to aldehydes by means of lithium aluminum hydride has in fact only recently proven of synthetic value, and then mainly for highly hindered nitriles.[7] Thus treatment of the nitrile ketal **29**[8] with 0.5 molar equiv of that hydride at room temperature followed by carefully controlled hydrolysis of the intermediate imine afforded aldehyde **30** admixed with small amounts of starting material and amine. Though the aldehyde was isolated for characterization, in practice the crude product was used for further elaboration. Condensation of that crude aldehyde with the ylide obtained from triethyl phosphonoacetate (sodium hydride) afforded the acrilic ester **31** as an oil whose NMR spectrum suggested that this consisted of a single isomer of the desired product. This intermediate was then subjected in turn to catalytic reduction, saponification, and deketalization to give the desired keto acid **32** as a crystalline compound. The intermediates were all characterized by spectral means.

Cyclization of the keto acid **32** to the spiro diketone **33** was again accomplished by means of liquid hydrogen fluoride (Scheme IV). Treatment of that diketone with 1 equiv of neopentyl glycol under conditions for ketal formation resulted in selective reaction at the alicyclic ketone to afford **34** (ν_{max} 1680 cm^{-1}). This last was then converted to the monoketone **36** by first reduction under Wolff–Kishner conditions and the removal of the protecting group. Reduction of the ketone by means of sodium borohydride in this case afforded a mixture of the isomeric alcohols. The stereochemistry in this series can thus be assigned in relatively straightforward manner. Chromatographic separation gave first 6.0% of the axial alcohol (NMR δ 4.1, $W/_{1/2}$ = 7 Hz) followed by 75.6% of the equatorial isomer (NMR δ 3.85, $W/_{1/2}$ = 14 Hz).

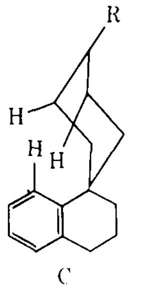
Examination of Dreiding models reveals conformers A (and B) to be relatively free of nonbonding hydrogen–hydrogen interactions; conformer C, on the other hand, shows



A

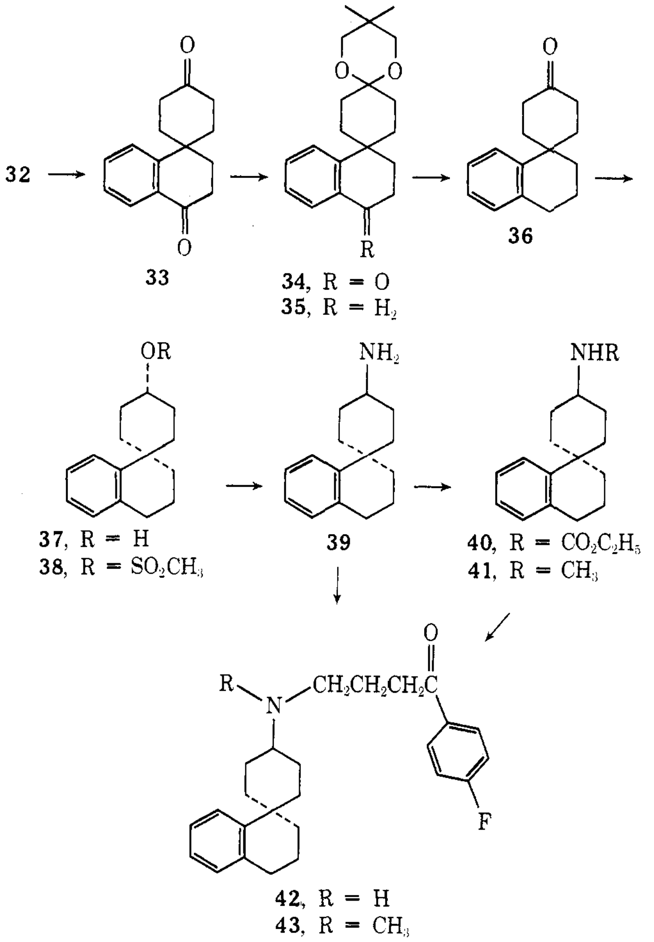


B



C

Scheme IV



serious interaction between the proton on the peri position of the teralin with the axial hydrogens at the 3 position of the cyclohexane ring. These considerations lead us to assign the structure A (R = OH) to the major alcohol. The alcohol was then taken on to the amine **39** via its mesylate (**38**) and azide. The inversion which accompanies the displacement step will, of course, cause that amine and its derivatives to have the stereochemistry depicted by B. Even in the event that these compounds would undergo a flip interconversion of the type described above, the *relative* stereochemistry remains unchanged. The primary amine was then converted to its carbamate **40** by means of ethyl chloroformate; reduction of the urethane with lithium aluminum hydride afforded the *N*-methyl derivative **41**. Both the primary and secondary amines were then converted to the butyrophenone derivatives (**42, 43**) exactly as in the case of **22**.

Experimental Section[9]

4-Benzyl-4-hydroxymethylcyclohexan-1-one Cyclic Ethylene Acetal (6). A solution of 22.3 g (0.077 mol) of methyl 4-benzyl-4-carbomethoxycyclohexanone ethylene acetal in 220 ml of THF was added to 3.0 g of $LiAlH_4$ in 30 ml of THF. The mixture was stirred at reflux for 5.5 hr and then cooled in ice. There was added in turn 3 ml of H_2O, 3 ml of 15% NaOH, and 9 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. The residue was recrystallized from CH_2Cl_2–Skellysolve B (SSB) to give 18.8 g (93%) of the alcohol: mp 76–78°; NMR δ 1.6 (m, 8, CH_2), 2.68 (s, 2, $ArCH_2$), 3.32 (d, J = 5 Hz, 2, CHOH), 3.90 (s, 4, ketal), 7.25 (s, 5, ArH).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: 73.08; H, 8.65.

4-Benzyl-4-hydroxymethylcyclohexan-1-one Cyclic Ethylene Acetal Methanesulfonate (7). To an ice-cold solution of 18.8 g (0.072 mol) of the alcohol in 100 ml of pyridine there was added 19 ml of CH_3SO_2Cl. Following 5.5 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 with H_2O, ice-cold 2.5 *N* HCl, H_2O, saturated $NaHCO_3$, and brine. The residual solid was recrystallized from CH_2Cl_2–SSB to give 21.1 g (86%) of mesylate: mp 94–97°; NMR δ 1.60 (m, 8, CH_2), 2.68 (s, 2, $ArCH_2$), 2.95 (s, 3, SO_2CH_3), 2.83 (s, 2, -CH_2OSO_2), 2.85 (s, 4, ketal), 7.20 (s, 5, ArH).

Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.97; H, 7.11. Found: C, 60.00; H, 7.17.

1-Benzyl-4-oxocyclohexaneacetic Acid Cyclic Ethylene Acetal (9). A mixture of 18.6 g (0.055 mol) of the mesylate and 18 g of KCN was heated in 200 ml of HMPA overnight in an oil bath at 145°. The resulting gel was then allowed to cool, diluted to 800 ml with H_2O, and extracted with C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 1 l. of silica gel (elution with 25% EtOAc in SSB). Those fractions which were similar by TLC were combined and heated overnight with 14.5 g of KOH in 105 ml of ethylene glycol. The mixture was then allowed to cool, diluted with H_2O, and washed once with Et_2O. The aqueous layer was then covered with Et_2O and cautiously acidified. The organic layer was separated, washed with brine, and taken to dryness. The residue was recrystallized from cyclohexane to give 12.3 g (77%) of acid, mp 116–118°. The analytical sample melted at 118–120°: NMR δ 1.65 (s, 8, CH_2), 2.26 (s, 2, CH_2CO_2H), 2.80 (s, 2, $ArCH_2$), 4.0 (s, 4, ketal), 7.31 (s, 5, ArH).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.50; H, 7.83.

1-Benzyl-4-oxocyclohexaneacetic ACID (10). A solution of 12.3 g (0.042 mol) of the ketal and 18 ml of 2.5 *N* HCl in 180 ml of Me_2CO was stirred at room temperature for 62 hr. The bulk of the solvent was 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 Et_2O–SSB to give 7.94 g (76%) of product: mp 85–87°; analytical sample, mp 91–92°; ir 1720, 1680, 1270, 1230, and 1175 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.58.

Spiro[cyclohexane-1,2′(1′*H*)-naphthalene]-4,4′(3′*H*)-dione (11). Hydrogen fluoride (200 ml) was added from an inverted cylinder to 34.58 g (0.14 mol) of the keto acid. Following 48 hr standing at room temperature the residual syrup was poured into saturated aqueous $NaHCO_3$. Sufficient solid $NaHCO_3$ was then added to neutralize the mixture. The precipitated gum was extracted with methylene chloride. These extracts were washed in turn with water and brine and taken to dryness. The residue was chromatographed over 4 l. of silica gel (elution with 20% acetone in SSB) to afford 19.19 g (60%) of product, mp 157–159°.

A small sample was recrystallized from acetone–SSB to afford diketone: mp 158–160°; NMR δ A_2B_2 pattern centered at 2.12 (8, cyclohexanone), 2.72 (s, 2, $ArCH_2$), 3.10 (s, 2, $COCH_2Ar$), 7.48 (m, 3, ArH), 8.05 (m, 1, ArH); ir 1710, 1675, 1595, 1285, and 775 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; mol wt, 228. Found: C, 78.69; H, 7.31; mol wt, 228.

Spiro[cyclohexane-1,2′(1′*H*)-naphthalene]-4,4′(3′*H*)-dione Cyclic 4-(Ethylene Acetal) (12). A mixture of 2.65 g (0.012 mol) of diketone, 0.72 g (0.65 ml) of ethylene glycol, and 0.20 g of *p*-TSA in 100 ml of C_6H_6 was heated at reflux under a Dean-Stark trap for 4.5 hr. The mixture was allowed to cool, washed with $NaHCO_3$ and brine, and taken to dryness. The residue was chromatographed on 300 ml of silica gel (elution with 25% EtOAc–SSB). The crystalline fractions were combined and recrystallized from Et_2O–SSB. There was obtained 2.20 g (70%) of monoketal: mp 90–91.5°; ir 1685, 1290, 1115, 1100, and 770 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.00; H, 7.66.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-one Cyclic Ethylene Acetal (13). A mixture of 2.20 g (0.0081 mol) of the ketone, 1.2 ml of $N_2H_4 \cdot H_2O$, and 1.6 g of KOH in 20 ml of ethylene glycol was heated at reflux for 1 hr. Solvent was then removed by distillation to bring the temperature to 200°, and reflux continued for 17 hr. The mixture was then poured into H_2O and this was extracted with Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether to give 1.86 g (88%) of product: mp 79–81°; NMR δ 2.60 (m, 10, CH_2), 2.62 (s, 2, $ArCH_2$), ~2.78 (m, 2, $ArCH_2CH_2$), 4.0 (s, 4, ketal), 7.08 (s, 4, ArH).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.14; H, 8.72.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-ol (19). A mixture of 1.86 g (0.0072 mol) of the ketal and 2 ml of 2.5 *N* HCl in 40 ml of Me_2CO was heated at reflux overnight. The bulk of 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 to afford the ketone as an oil whose NMR spectrum was in accord with the structure.

A solution of the residue in 50 ml of 95% *i*-PrOH was treated with 1.0 g of $NaBH_4$. At the end of 5 hr the solvent was removed under vacuum and the residue worked up as above. The crude product was chromatographed on 170 ml of silica gel (elution with CH_2Cl_2). There was obtained first 0.24 g of recovered ketal. The product fractions were combined and recrystallized from SSB to give 0.65 g (42%) of alcohol: mp 78–82°; NMR δ 1.5 (m, 10, CH_2), 2.6 (m, 4, $ArCH_2$), 3.56 (seven-line pattern, 1, CHOH), 7.0 (s, 4, ArH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32; mol wt, 216. Found: C, 83.37; H, 9.43; mol wt, 216.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-ol Methanesulfonate (20). To an ice-cold solution of 2.16 g (0.01 mol) of the alcohol in 10 ml of pyridine there was added 2 ml of CH_3SO_2Cl. Following 4 hr in the cold the mixture was poured onto ice–H_2O. The solid was collected on a filter and recrystallized from Et_2O–petroleum ether. There was obtained 2.52 g (86%) of mesylate: mp 66–69°; NMR δ 1.7 (m, 10, CH_2), 2.7 (m, 4, $ArCH_2$), 3.0 (s, 3, SO_2CH_3), 4.70 (seven-line pattern, 2, CHO), 7.05 (s, 4, Ar H).

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.38; H, 7.54.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-amine Hydrochloride (22). A mixture of 2.52 g (0.0085 mol) of the mesylate and 2.5 g of NaN_3 in 25 ml of DMF was heated overnight in an oil bath at 90°. The solvent was then removed under vacuum and the residue taken up in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. A solution of the residue in 60 ml of THF was added to 0.35 g of $LiAlH_4$ in 10 ml of THF. Following 4 hr of stirring at room temperature, the mixture was cooled in ice and treated with 0.35 ml of H_2O, 0.35 ml of 15% NaOH, and 1.05 ml of H_2O. The inorganic gel was collected on a filter and the filtrate was taken to dryness. A solution of the residue in Et_2O was treated with 6 *N* HCl in Et_2O. The resulting solid was recrystallized from CH_2Cl_2–EtOAc to give 1.65 g (77%) of product: mp 208–211°; ir ca. 2950 br, 1615, 1495, 1035, and 760 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.75; H, 8.83; N, 5.58. Found: C, 71.52; H, 8.79; N, 5.54.

4′-Fluoro-4-[(3′,4′-dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-yl)amino]butyrophenone Hydrochloride (23). The free base from 1.65 g (0.0066 mol) of the amine hydrochloride, 1.34 g of KI, 2.06 g of K_2CO_3, and 1.90 g of the neopentyl glycol acetal of 4-chloro-*p*-fluorobutyrophenone in 35 ml of DMF was heated in an oil bath at 90°. At the end of 18 hr the bulk of the solvent was removed under vacuum. The residue was dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue and 10 ml of 2.5 *N* HCl in 20 ml of MeOH was stirred at room temperature for 4 hr. The MeOH was then removed under vacuum and the solid collected on a filter. This was recrystallized twice from CH_2Cl_2–EtOAc to afford 1.07 g (39%) of the butyrophenone: mp 182–184°; ir 2760, 1690, 1600, 1245, 1160, 835, and 755 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 72.18; H, 7.51; N, 3.37; mol wt, 379. Found: C, 72.20; H, 7.53; N, 3.47; mol wt, 379.

(3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-yl)piperidine Hydrochloride. Isomer A (24). A mixture of the free base prepared from 1.81 g (0.0072 mol) of the free base **22**, 2.34 g of 1,5-diiodopentane, and 2.0 g of potassium carbonate in 20 ml of ethanol was heated at reflux for 17 hr. The solvent was then removed under vacuum and the residue partitioned between water and ether. The organic layer was washed with water and brine and taken to dryness. The residue was dissolved in a small amount of ether and treated with excess 3 *N* ethereal hydrogen chloride. The precipitated solid was recrystallized twice from methanol–ethyl acetate to afford 0.78 g (34%) of product: mp 290–293°; ir 2640, 2500, 2420, 1495, 745, and 735 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}ClN$: C, 75.08; H, 9.45; N, 4.38. Found: C, 75.07; H, 9.56; N, 4.23.

3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-one Oxime (25). A mixture of 8.33 g (0.039 mol) of the ketone, 5.40 g of hydroxylamine hydrochloride, and 10.7 g of K_2CO_3 in 100 ml of methanol was heated at reflux for 6 hr. The solvent was then removed under vacuum and the residue partitioned between methylene chloride and water. The organic layer was washed with water and brine and taken to dryness. The residue was recrystallized from methylene chloride–Skellysolve B to give 8.52 g (95%) of product, mp 105–106.5°.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.36; H, 8.31; N, 6.05.

(3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-yl)amine Hydrochloride. Isomeric Mixture (27). To a solution of 2.50 g (0.011 mol) of the oxime in 12.5 ml of pyridine there was added 2.5 ml of acetic anhydride. At the end of 6 hr the solution was poured into ice water. The precipitated gum was extracted with ether and the organic layer washed in turn with water, 2.5 *N* hydrochloric acid, aqueous sodium bicarbonate, and brine. The extract was then taken to dryness to afford the product as a viscous gum whose NMR spectrum is in accord with the structure.

An ice-cold solution of the crude oxime acetate in 60 ml of THF was treated with 12 ml of *N*-diborane in THF. At the end of 6 hr there was added 1 ml of water; as soon as effervescence ceased, the bulk of the solvent was removed under vacuum. A mixture of the residue and a small amount of ether was stirred with 50 ml of 2.5 *N* hydrochloric acid for 17 hr, and then made strongly basic. The mixture was extracted with ether; the organic layer was washed with water and brine and taken to dryness. A solution of the residue in ether was treated with a solution of 2.2 g of *p*-toluenesulfonic acid in the same solvent. The gummy precipitate was recrystallized several times from methylene chloride–ethyl acetate to give 1.58 g (34%) of product, mp 203–207°.

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.19; H, 7.54; N, 3.62. Found: C, 67.81; H, 7.43; N, 3.39.

(3′,4′-Dihydrospiro[cyclohexane-1,2′(1′*H*)-naphthalen]-4-yl)piperidine Hydrochloride (24, 28). A mixture of the free base from 1.58 g (0.0042 mol) of the tosylate, 1.36 g of 1,5-diiodopentane, and 1.16 g of potassium carbonate in 10 ml of ethanol was heated at reflux for 17 hr. The solvent was removed under vacuum and the residue partitioned between water and ether. The organic layer was washed with water and brine and taken to dryness. A solution of the residue in ether was treated with excess 3 *N* ethereal hydrogen chloride.

The precipitated solid was recrystallized twice from methanol–ethyl acetate to give 0.40 g (30%) of isomer A, mp 290–293°, mmp with authentic material 290–293°.

The solid which was obtained on taking the mother liquors to dryness was recrystallized several times from methylene chloride–ethyl acetate to give 0.37 g (28%) of isomer B: mp 260–263°; ir 2640, 2610, 2490, 2410, 1495, 1485, and 750 cm^{-1}; mmp with isomer A 255–258°.

Anal. Calcd for $C_{20}H_{30}ClN$: C, 75.08; H, 9.45; N, 4.38. Found: C, 75.02; H, 9.66; N, 4.71.

4-Oxo-1-phenylcyclohexanecarboxaldehyde Cyclic 4-(Ethylene Acetal) (30). To a suspension of 0.16 g (0.0041 mol) of $LiAlH_4$ in 10 ml of THF was added 2.0 g (0.0082 mol) of cyano ketal in 100 ml of THF over 15 min. The mixture was stirred at room temperature for 1.75 hr and cooled in an ice bath. There was added in turn 0.16 ml of H_2O, 0.16 ml of 15% NaOH, and 0.48 ml of H_2O. The inorganic gel was collected on a filter and rinsed with Et_2O and the combined filtrates taken to dryness.

The residue in 30 ml of THF and 3 ml of 2.5 *N* HCl was stirred at room temperature for 15 min, treated with 1.0 g of $NaHCO_3$, and taken to dryness under vacuum. Et_2O was added to the residue, and the organic fraction was separated and taken to dryness. This material proved suitable for use in the next step.

The residue was chromatographed on silica gel (elution with 1% EtOAc–CH_2Cl_2) and the more polar crystalline fractions combined to yield 0.87 g (86.4%) of aldehyde: mp 59–64°; ir 1710, 1110, 1030, 825, and 700 cm^{-1}.

The analytical sample melted at 68.5–71°.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.43; H, 7.56.

4-Oxo-1-phenylcyclohexanepropionic Acid (32). To a solution of 4.74 g (0.021 mol) of triethyl phosphonoacetate in 60 ml of THF was added 0.89 g of 57% NaH. Following 10 min stirring at room temperature there was added a solution of 5.20 g (0.021 mol) of the aldehyde in 60 ml of THF. The solution was stirred at reflux for 4 hr and at room temperature for 18 hr. The bulk of the solvent was removed under vacuum, and the residue was dissolved in Et_2O and H_2O. The organic fraction was washed with H_2O and brine and taken to dryness. The residue was chromatographed over 700 ml of silica gel (elution with 1600 ml of SSB, then 4 l. of 5% Me_2CO–SSB). Those uv-absorbing fractions alike by TLC were combined to yield 6.38 g (96%) of acrylic ester as a gum.

A mixture of 6.38 g (0.020 mol) of the ester obtained above, 0.63 g of 10% Pd/C, and 150 ml of EtOAc was shaken under an atmosphere of H_2 until the theoretical amount was consumed. The catalyst was collected on a filter and the filtrate taken to dryness to yield 6.38 g (~100%) of product as an oil.

A solution of 6.38 g (0.020 mol) of the reduced product and 8.0 ml of 50% NaOH in 80 ml of MeOH was heated at reflux for 20 hr. The bulk of the MeOH was removed under vacuum, H_2O was added to the residue, and the latter was washed with Et_2O. The aqueous fraction was then made strongly acidic. The precipitated material was extracted with Et_2O and the combined extracts washed with brine and taken to dryness.

The residue was dissolved in 50 ml of Me_2CO and 5.0 ml of 2.5 *N* HCl and allowed to stand at room temperature for 48 hr. The solution was taken to near dryness under vacuum and the residue dissolved in H_2O and Et_2O. The organic fraction was washed with H_2O and brine and taken to dryness. The residue was recrystallized from CH_2Cl_2–SSB to yield 1.70 g (34.5%) of keto acid: mp 143–144.5°; ir 1708, 1698, 1230, and 780 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.04; H, 7.40.

Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4,4′(3′*H*)-dione (33). HF (5.0 ml) was distilled onto 5.0 g (0.0203 mol) of the keto acid and the resulting solution allowed to stand at room temperature for 20 hr. The residue was dissolved in Et_2O, washed with H_2O, saturated aqueous $NaHCO_3$, and brine, and taken to dryness. The residue was recrystallized from Et_2O to give 1.13 g (28%) of spiro diketone: mp 145.5–148°; ir 1705, 1685, 1595, 1290, 1275, and 780 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.23; H, 7.88. Found: C, 78.39; H, 7.18.

Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4,4′(3′*H*)-dione 4-2,2-Dimethylpropylene Acetal (34). A solution of 3.19 g (0.014 mol) of the spiro diketone, 1.45 g (0.014 mol) of 2,2-dimethylpropanediol, and 0.06 g of *p*-TSA in 57 ml of benzene was heated at reflux under a Dean-Stark trap for 5.5 hr. The solution was washed with saturated aqueous $NaHCO_3$ and brine and taken to dryness. The residue was chromatographed over 400 ml of Florisil (elution with 7.5% EtOAc–SSB). The crystalline fractions were combined to yield 3.29 g (75%) of product, mp 136–138°. An analytical sample from an earlier run recrystallized from Et_2O–SSB melted at 138.5–142°; ir 1690, 1295, 1115, 930, 870, and 780 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.49; H, 8.38.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one 2,2′-Dimethylpropylene Acetal (35). A solution of 3.63 g (0.0115 mol) of ketone, 1.54 ml of hydrazine hydrate, and 2.23 g of KOH in 28 ml of ethylene glycol was heated at reflux. Distillate was collected until the pot temperature rose to 200° and reflux was continued for 18 hr. The mixture was poured into H_2O and a precipitated material extracted with Et_2O. The combined extracts were washed with H_2O and brine and taken to dryness. The residue was recrystallized from petroleum ether to yield 2.39 g (69.5%) of product: mp 109–111°; ir 1110, 1020, 910, 860, 760, and 755 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.95; H, 9.51.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-one (36). A mixture of 2.39 g (0.008 mol) of ketal and 2.4 ml of 2.5 *N* HCl in 24 ml of Me_2CO was stirred at room temperature for 6 hr. H_2O (15 ml) was added and the bulk of the Me_2CO was removed under vacuum. Et_2O was added to the residue, and the organic fraction was washed with H_2O, saturated aqueous $NaHCO_3$, and brine and taken to dryness. The residue was recrystallized from petroleum ether to yield 1.19 g (70%) of ketone, mp 115–120°. An analytical sample from a previous run melted at 120.5–123°; ir 1710, 1495, 1160, 765, and 735 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.83; H, 8.48.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ol (37). To a partial solution of 5.10 g (0.024 mol) of ketone in 105 ml of 95% EtOH was added 2.59 g of $NaBH_4$ and the mixture was stirred at room temperature for 4 hr. The bulk of the solvent was removed under vacuum and H_2O added to the residue. A precipitated material was extracted with Et_2O and the combined extracts washed with H_2O and brine and taken to dryness. The residue was recrystallized once from SSB and then chromatographed over 500 ml of silica gel (elution with 10% Me_2CO–SSB). On the basis of TLC the less polar fractions were combined and recrystallized from C_6H_6–cyclohexane to give 0.31 g (6.0%) of product: mp 144.5–146°; NMR δ 4.1 (*m*, $W_{1/2}$ = 7 Hz, 1, CHOH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.53; H, 9.61.

On the basis of melting point the polar fractions were combined and recrystallized from SSB to give 3.89 g (74.9%) of product: mp 80–83°; NMR δ 3.85 (m, $W_{1/2}$ = 12 Hz, 1, CHOH).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.47; H, 9.55.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ol Methanesulfonate (38). To an ice-cooled solution of 3.89 g (0.018 mol) of the alcohol in 40 ml of pyridine was added 4.0 ml of methanesulfonyl chloride. The mixture was allowed to stand in the cold for 6 hr and then diluted with H_2O. A precipitated material was extracted with Et_2O and the combined extracts washed with ice-cold 2.5 *N* HCl, H_2O, saturated aqueous $NaHCO_3$, and brine and taken to dryness. The residue was recrystallized from cyclohexane to yield 5.0 g (94.3%) of mesylate: mp 118–120°; ir 1345, 1170, 980, 935, 865, and 760 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53; S, 10.89. Found: C, 65.17; H, 7.61; S, 10.70.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ylamine Hydrochloride (39). A mixture of 5.0 g (0.017 mol) of the mesylate and 5.0 g of NaN_3 in 50 ml of DMF was heated in an oil bath at 90° for 20 hr. The bulk of the solvent was removed at vacuum pump pressure and the residue dissolved in H_2O and C_6H_6. The organic fraction was washed with H_2O and brine and taken to dryness to yield the crude azide as an oil.

A solution of the above in 75 ml of THF was added to a suspension of 0.65 g of $LiAlH_4$ in 8 ml of THF, stirred at room temperature for 5.5 hr, and cooled in an ice bath. There was added in turn 0.65 ml of H_2O, 0.65 ml of 15% NaOH, and 1.95 ml of H_2O. The resulting gel was collected on a filter and washed with Et_2O, and filtrates were taken to dryness. The residue was dissolved in a small amount of Et_2O and an excess of 6.4 *N* HCl in Et_2O added. The precipitate was collected on a filter and recrystallized from MeOH–EtOAc to yield 1.76 g (40.5%) of amine salt: mp 271–273°; ir 3000, 1590, 1505, 1490, 755, and 725 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClN \cdot \frac{1}{4}H_2O$: C, 70.29; H, 8.85; N, 5.47. Found: C, 70.48; H, 8.78; N, 5.55.

Ethyl Spiro[cyclohexane-1,1′(2′*H*)-naphthalene]-4-carbamate (40). To an ice-cooled solution of the amine free base [prepared from 1.53 g (6.1 mmol) of the amine salt] in 12 ml of pyridine was added 0.95 ml of ethyl chloroformate. The mixture stood in the cold for 5 hr and then was poured into ice–H_2O. A solid precipitate was collected on a filter and recrystallized from CH_2Cl_2–C_6H_{12} to yield 1.36 g (77.7%) of the carbamate: mp 163.5–165°; ir 3270, 1695, 1335, 1090, and 760 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: 74.91; H, 8.77; N, 4.83.

3′,4′-Dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-yl-*N*-methylamine Hydrochloride (41). To a suspension of 0.22 g (5.8 mmol) of $LiAlH_4$ in 10 ml of THF was added a solution of 1.30 g (4.5 mmol) of the carbamate. The mixture was stirred at reflux for 6 hr and at room temperature for 18 hr, and then cooled in an ice bath. There was added in turn 0.22 ml of H_2O, 0.22 ml of 15% NaOH, and 0.66 ml of H_2O. The resulting inorganic gel was collected on a filter and rinsed with Et_2O and the filtrates were taken to dryness. The residue was dissolved in a small amount of Et_2O and treated with an excess of 6.4 *N* HCl in Et_2O. The resulting precipitate was collected on a filter and recrystallized from MeOH–EtOAc to yield 0.81 g (52.7%) of the secondary amine, mp 285–286°.

Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.25. Found: C, 72.60; H, 9.16; N, 5.35.

4′-Fluoro-4-(3′,4′-dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-ylamino)butyrophenone Hydrochloride (42). A mixture of the free base [prepared from 1.0 g (3.97 mmol) of the amine salt], 0.81 g of KI, 1.24 g of K_2CO_3, and 1.14 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal in 20 ml of DMF was heated together in an oil bath at 90° for 20 hr. The solvent was removed under vacuum and the residue dissolved in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue, 8.0 ml of 2.5 *N* HCl, and 16 ml of

MeOH was stirred at room temperature for 2 hr and the bulk of the MeOH removed under vacuum. A residual suspended solid was collected on a filter, washed with Et_2O, and recrystallized from MeOH–EtOAc to give 0.65 g (39.5%) of the butyrophenone: mp 194–197°; ir 2760, 2720, 1685, 1600, 835, and 770 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}ClFNO$: C, 72.18; H, 7.51; N, 3.37. Found: C, 72.42; H, 7.66; H, 3.14.

4′-Fluoro-4-(3′,4′-dihydrospiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4-yl-*N*-methylamino)butyrophenone Hydrochloride (43). A mixture of the amine free base [prepared from 0.81 g (3.06 mmol) of the amine salt], 0.63 g of KI, 0.96 g of K_2CO_3, and 0.87 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene acetal in 15 ml of DMF was heated together in an oil bath at 90° for 20 hr. The solvent was removed under vacuum and the residue dissolved in H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue, 6.0 ml of 2.5 *N* HCl, and 12 ml of MeOH was stirred at room temperature for 1.5 hr and the bulk of the MeOH was removed under vacuum. A residual suspended solid was collected on a filter, washed with Et_2O, and recrystallized from MeOH–EtOAc to yield 0.59 g (44.8%) of the butyrophenone: mp 204–205.5°; ir 2660, 1675, 1225, 1210, 1150, and 755 cm^{-1}.

Anal. Calcd for $C_{26}H_{33}ClFNO$: C, 72.62; H, 7.74; N, 3.26. Found: C, 72.69; H, 7.93; N, 3.03.

Registry No.—5, 56868-61-2; **6,** 56868-62-3; **7,** 56868-63-4; **9,** 56868-64-5; **10,** 56868-65-6; **11,** 56868-66-7; **12,** 56868-67-8; **13,** 56868-68-9; **19,** 56868-69-0; **20,** 56868-70-3; **22,** 56868-71-4; **23,** 56868-72-5; **24,** 56868-73-6; **25,** 56868-74-7; *cis*-**27** tosylate, 56868-76-9; *trans*-**27** tosylate, 56868-78-1; **28,** 56868-79-2; **29,** 51509-98-9; **30,** 56327-24-3; **32,** 2572-26-1; **33,** 56868-88-3; **34,** 56868-89-4; **35,** 56868-90-7; **36,** 56868-91-8; *cis*-**37,** 56868-80-5; *trans*-**37,** 56868-81-6; **38,** 56868-82-7; **39,** 56868-83-8; **40,** 56868-84-9; **41,** 56868-85-0; **42,** 56868-86-1; **43,** 56868-87-2; 4-chloro-*p*-fluorobutyrophenone neopentyl glycol acetal, 36714-65-5; 2,2-dimethylpropanediol, 126-30-7.

References and Notes

(1) D. Lednicer and D. E. Emmert, *J. Org. Chem.*, preceding paper in this issue.

(2) D. Lednicer, D. E. Emmert, R. A. Lahti, and A. D. Rudzik, *J. Med. Chem.*, **16**, 1251 (1973).

(3) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden Day, San Francisco, Calif., 1964, p 80.

(4) B. V. Cheney, *J. Am. Chem. Soc.*, **90**, 5386 (1968).

(5) It is possible that the reaction involves reduction of each conformer of the ketone **14** stereoselectivity to the equatorial amine. This still leaves open the question why reduction of the ketone by sodium borohydride appears to proceed only via the more stable conformer.

(6) L. Friedman, Abstract of Papers, 116th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept. 1949, p 5M.

(7) G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, **93**, 4945 (1971).

(8) D. Lednicer, D. E. Emmert, A. D. Rudzik, and B. E. Graham, *J. Med. Chem.*, **18**, 593 (1975).

(9) 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. NMR spectra (100 MHz) were determined in deuteriochloroform on a Varian X6100 spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental analyses.

Acid-Catalyzed Rearrangements of Polymethylnaphthalenes

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α,β-Methyl migrations were found to occur smoothly in trifluoroacetic acid in seven polymethylnaphthalenes with methyl substituents in peri positions and with at least one adjacent β position unsubstituted. For example, 1,2,3,4,5,8-Me_6-naphthalene gave the 1,2,3,4,5,7 isomer, which, in turn, gave the 1,2,3,4,6,7 isomer; 1,4,5,8-Me_4-naphthalene gave the 1,3,5,8 isomer, which further gave a mixture (10:1) of 1,3,5,7 and 1,4,6,7 isomers. In naphthalenes without peri position methyl groups, little rearrangement occurred but, instead, intermolecular methyl and hydride transfer took place at slow rates; e.g., 1,2,3,4-Me_4-naphthalene in CF_3COOH gave 1,2,3-Me_3- and a Me_5-naphthalene as well as 1,2,3,4-tetrahydro-5,6,7,8-Me_4-naphthalene; Me_8-naphthalene, though with peri position methyl groups, gave 1,2,3,4,5,6,7-Me_7- and 1,2,3,5,6,7-Me_6-naphthalene. The basicity of polymethylnaphthalenes, structures of naphthalenium ions, and methyl migrating forces were discussed in terms of peri dimethyl interaction. A kinetic study of the rates of rearrangement for seven naphthalenes showed that the rates do not always follow a first-order rate equation.

It has been well known that introduction of two bulky groups in the peri position of a naphthalene causes steric crowding (so-called peri interaction)[1] as most evident in the crystal structure of octamethyl- and octachloronaphthalene.[2] Hart and one of the authors (A.O.)[3] observed the formation of stable naphthalenium ions of octamethylnaphthalene and 1,2,3,4,5,8- and 1,2,3,4,5,6-hexamethylnaphthalene by NMR in trifluoroacetic acid (CF_3COOH), and suggested that the observed increase in basicity is characteristic of naphthalenes with methyl substituents in peri positions and that the primary force to increase the stability of carbocations must be the relief of steric strain in peri interaction. In the present study, we have found that a smooth migration of peri methyl groups can be induced from naphthalenium ions where the β position adjacent to the protonated peri position is unsubstituted. On the assumption that the peri interaction not only increases the basicity of a naphthalene but also accelerates the migration of peri substituents, we have carried out the experiments reported here in order to clarify the characteristics of this effect.

Protonation and rearrangements in carbocyclic systems promoted by the accompanying relief of steric strain have often been encountered.[4] Additionally, methyl migration in methylbenzenes as well as in mono- and dimethylnaphthalenes has been known to occur at a slow rate measurable only in such strong acids as $HF-BF_3$ or superacids.[5] Our work, however, found a significant difference in the ease of methyl migration between polymethylnaphthalenes with and without methyl substituents in peri positions; for example, the former naphthalenes undergo methyl rearrangement readily in such relatively weak acids as CF_3COOH or HCl, but the latter do not. It was also found even among peri-substituted naphthalenes that the rate of rearrangement depends markedly upon the number and position of methyl substituents. Therefore, with the purpose of reveal-