Spiro Piperidines. 1. Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones, Spiro[isobenzofuran-1(3*H*),4′-piperidines], and Spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines][1]

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Improved synthetic procedures for spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones (**3**) and spiro[isobenzofuran-1(3*H*),4′-piperidines] (**5**) are described. Elaboration of *o*-bromobenzyl mercaptan by conversion to *o*-lithiobenzyl mercaptide can be effected at very low temperature (−100 °C) without appreciable alkylation of mercaptide by *n*-butyl bromide, formed by exchange with *n*-butyllithium. Preparations of new systems including spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines] (**27**) and imines of spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (**13**) are described.

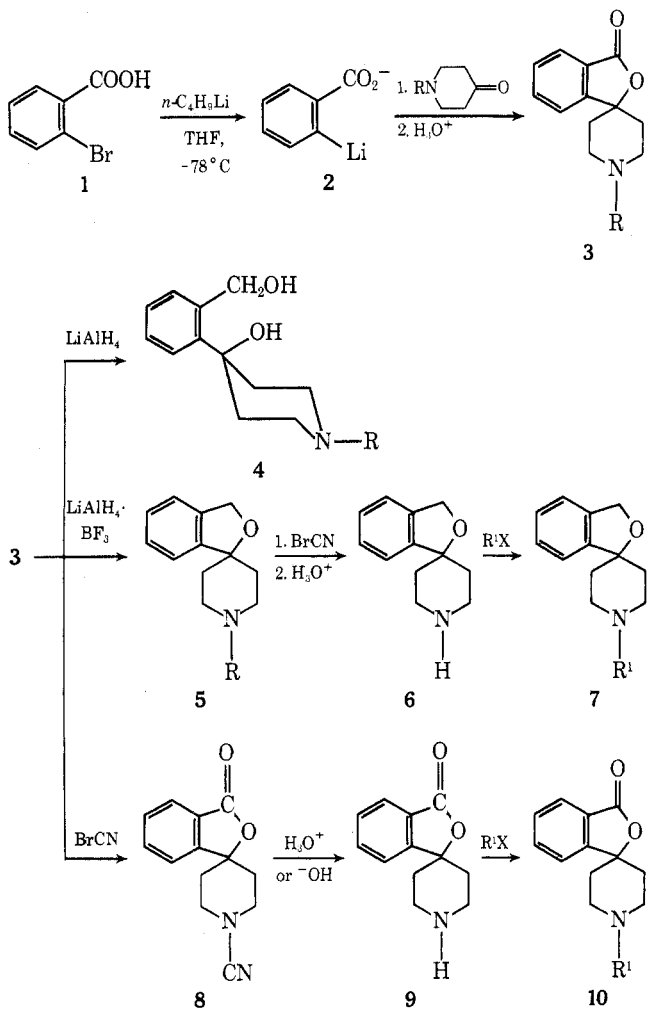
The preparation of the spiro[isobenzofuran-1(3*H*),4′-piperidine] ring system was recently described for the first time.[3] Intermediate spirophthalides of type **3** were prepared by initial reaction of the magnesium derivative of 2-(2-bromophenyl)-4,4′-dimethyloxazoline (Meyers method[4]) with *N*-alkylpiperidones, a process which gave low yields (~35%) because of competing enolization of the ketone, or, more conveniently, by initial reaction of the lithium salt of 2-lithio-*N*-phenylbenzamide[5] with the corresponding piperidones (~50% yield). We have had a continuing interest[2,3b] in this heterocyclic system and wish to report improved procedures for its preparation, as well as the syntheses of related materials including new sulfur analogues.

The sequence shown in Scheme I was developed as part of our elaboration of isomeric bromobenzoic acids by halogen–metal exchange at low temperature,[6] and has the advantages that (a) no blocking of the carboxylic acid group other than conversion to carboxylate is required, (b) enolization of the ketone is not a serious side reaction with lithium reagents since good yields of phthalides **3** result, and (c) the method can theoretically be extended to a variety of substituted *o*-bromobenzoic acids since it is now known that at very low temperature many reactive groups (COO^-,[6] NO_2,[7] CN,[8] CH_2Cl[9]) do not react with *n*-butyllithium. The ketones employed in this work were cyclohexanone, *N*-methyl-4-piperidone, and tropinone; lactones prepared in this way are described in entries 1–3 of Table I.

Reduction of **3** (R = CH_3) with $LiAlH_4$ gave diol **4** in 86% yield while reduction with $LiAlH_4$ in the presence of boron trifluoride etherate[11] gave **5** (R = CH_3) in 76% yield. Phthalan **5** (R = CH_3) had previously been prepared[3] as its hydrochloride and was obtained in good yield by reduction of **3** (R = CH_3) with diborane. Similarily, reduction of lactone **11** (Table I) gave the corresponding spirotropane **12** (entry 7, Table I) in 81% yield. Both lactone **3** (R = CH_3) and phthalan **5** are efficiently demethylated in high yield (see Table I) to **9** and **6**, respectively, by reaction with cyanogen bromide[12] with subsequent removal of the *N*-cyano function by acid or base hydrolysis.

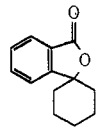
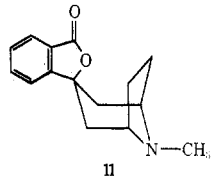
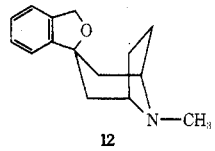
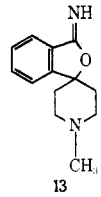
The sequence shown in Scheme I would appear to be the method of choice for the preparation of compounds of type **3–10** for those cases where starting bromo acids (**1**) are readily available. A modification of this sequence based on our reported utilization of 2-lithiobenzonitrile[8a] also provides ready access to the hitherto unknown imine derivatives of spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones. This concept was demonstrated by preparation of **13** (entry 9, Table I) in 72% yield from 2-lithiobenzonitrile and *N*-methyl-4-piperidone.

Scheme I



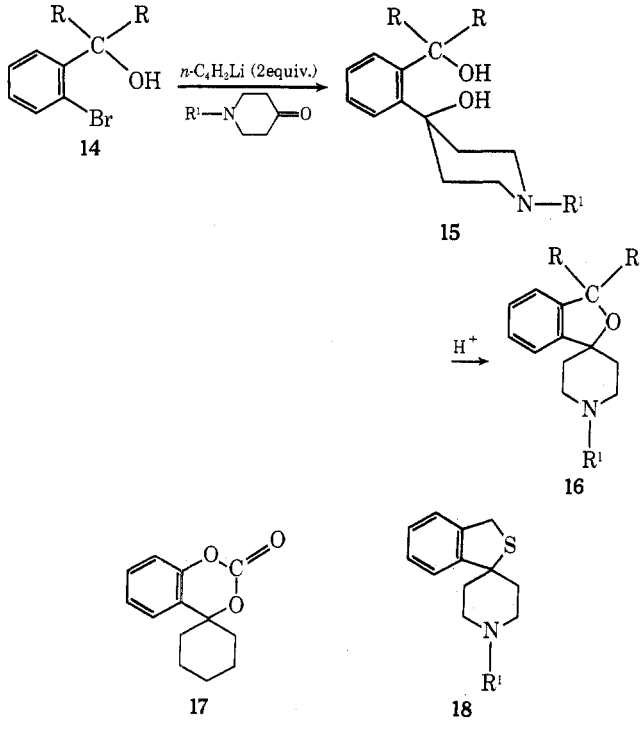
Prior to our development of low-temperature halogen–metal exchange for isomeric bromobenzoic acids,[6] we explored an alternate route to spiro[isobenzofuran-1(3*H*),4′-piperidines] (**16**), spirocarbonates (**17**), and the hitherto unknown spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines] (**18**) as illustrated in Scheme II. The route shown in Scheme II is an extension of that described[13] for the preparation of carbocyclic diols and phthalans. Diols **15**, together with related compounds prepared in this way, are shown in Table II.

Table I. Lactones and Phthalans from Scheme I[10]

Entry	Reactants	Product	Yield, %	Mp, °C
1	Cyclohexanone + **2**		69	81–82[a,b]
2	*N*-Methylpiperidone + **2**	**3** (R = CH_3)	61	151–152[c,d]
3	Tropinone + **2**	 **11**	58	134–135[e]
4	**3** (R = CH_3) + BrCN	**8**	77	182–183[c]
5	**8** + H_3O^+	**9**	83	132–133[c]
6	**3** + $LiAlH_4 \cdot BF_3$	**5**	82	78–80[f]
7	**11** + $LiAlH_4 \cdot BF_3$	 **12**	81	60–62[g]
8	**5** (R = CH_3) + BrCN then H_3O^+	**6**	76	84–86[f]
9	*o*-Bromobenzonitrile + *n*-C_4H_9Li (1 equiv) at −100 °C, then *N*-methylpiperidone	 **13**	72	96–99[a] [137–142 °C (0.03 Torr)]

[a] From ligroin (bp 60–90 °C). [b] $\nu_{C=O}$ 1740 cm^{-1}. [c] From $CHCl_3$–ligroin (bp 30–60 °C). [d] $\nu_{C=O}$ 1750 cm^{-1}; lit.[3a] mp 147–148 °C. [e] From H_2O. [f] By sublimation at 60–65 °C (0.02 Torr). [g] By sublimation of crude solid (mp 53–55 °C) at 50 °C (0.02 Torr).

Scheme II



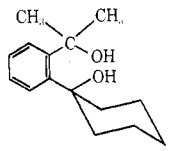
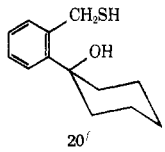
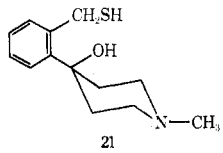
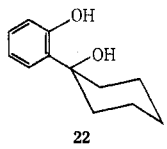
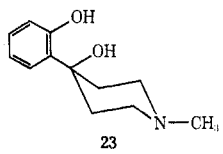
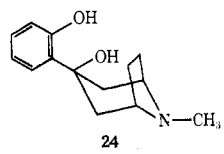
Attention should be called to the temperature sensitivity of the reaction involving halogen–metal exchange of 2-bromobenzyl mercaptan leading to **20** and **21** (entries 5 and 6, Table II). These reactions were carried out at −100 °C; at higher temperatures (−78 °C) the products were contaminated by products derived by butylation of mercaptide ion with *n*-butyl bromide formed during exchange with *n*-butyllithium. Such alkylation did not occur at −100 °C. The yields of phenols (entries 7–9), prepared by initial lithium–bromine exchange using *o*-bromophenol at −20 °C, were generally low; some dehydration of the tertiary alcohol occurred during processing. The alkenes formed in this way were prepared in high yield (see Experimental Section) by dehydration of **22–24** with 2 N sulfuric acid.

The cyclic carbonate **17** (Scheme II) was prepared in 43% yield by reaction of **22** (entry 7, Scheme II) with phosgene (THF at 0 °C); however, dehydration occurred in similar reactions with the amino diols **23** and **24** leading to alkenes and the corresponding carbonates were not obtained.

The hitherto unknown spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidine] (**18**) (Scheme II) as well as a number of related phthalides and phthalans were prepared by reaction of the corresponding mercapto alcohols or diols shown in Table II with mild acid; yields and conditions are summarized in Table III. While the sequence **14** → **15** → **16** gives excellent yields in some cases, and provides considerable latitude as to substitution (i.e., dialkylphthalans of type **28** and **29**, and sulfur analogues such as **25** and **27**), the sequence is not as convenient as that shown in Scheme I for the preparation of diols of type **4** or phthalans of type **5**.

A variety of alkyl or acyl derivatives of the demethylated spiro piperidine **6** and spiro piperidone **9** were also prepared

Table II. Diols and Related Materials from Scheme II[10]

Entry	Product	Yield, %	Mp (or bp), °C
1	**15** (R = H; R′ = CH_3)	51	138.5–140[a]
2	**15** (R = H; R′ = $CH_2C_6H_5$)	60	132–135.5[c]
3	**15** (R = R′ = CH_3)	71	130[d]
4	 **19**	70	152.5[e]
5	 **20**[f]	60	(110–113, 0.09 Torr)
6	 **21**	43	151–152[e]
7	 **22**	57–80	111–112[e]
8	 **23**	29	175–176[g] 169–170[h]
9	 **24**	20	168–169[h]

[a] From EtOH–C_6H_6. [b] The same product obtained in 86% yield from **3** was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C). [c] Hexane–acetone. [d] Ligroin (bp 30–60 °C). [e] $CHCl_3$–ligroin (bp 30–60 °C). [f] From *o*-bromobenzyl mercaptan, *n*-butyllithium (2 equiv) at −100 °C and ketone. [g] From acetone. [h] Analytical sample sublimed at 130 °C (0.02 Torr). [h] From acetone.

by alkylation or acylation; products, together with conditions employed, are shown in Table IV.

Experimental Section

Synthesis of Spiro Lactones. General Procedure. 1′-Methylspiro[isobenzofuran-1(3*H*)-4′-piperidin]-3-one (3, R = CH_3). *o*-Bromobenzoic acid (10.05 g, 0.05 mol) was added to a dry 300-ml three-necked flask equipped with an addition funnel, low temperature thermometer, nitrogen inlet, and mechanical stirrer. Dry THF (200 ml, distilled from $LiAlH_4$) was added and the solution was cooled to −78 °C in a dry ice–ether bath under positive N_2 pressure. *n*-Butyllithium (50.0 ml of 2.0 M solution in hexane, 0.10 mol) was slowly added (3 h) while maintaining the mixture below −70 °C and the resulting solution was stirred for an additional 2 h at −78 °C. Freshly distilled *N*-methyl-4-piperidone (7.9 g, 0.07 mol) in dry hexane (25 ml) was added over 30 min while maintaining the mixture below −70 °C. The mixture was allowed to warm to room temperature and was added to 300 ml of H_2O and 200 ml of ether. The basic layer was extracted with ether (five 100-ml portions) and was acidified with concentrated HCl (to pH 2–3) and extracted with ether. The acidic solution was boiled for 1 h and was then cooled (0–5 °C) and made alkaline (to pH 9–10) with cold aqueous NaOH. The cold solution was rapidly extracted with five 200-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O (100 ml), dried ($MgSO_4$), and concentrated to give 7.9 g of light yellow solid (mp 129–146 °C). Recrystallization of this product from $CHCl_3$–ligroin (bp 30–60 °C) gave 6.65 g (61% yield) of pure **3**[10] (R = CH_3), mp 151–152 °C, ir $\nu_{C=O}$ 1750 cm^{-1} (lit.[3a] mp 147–148 °C).

Lactones shown in entries 1–3 of Table I were prepared in a similar manner using the corresponding ketone and the appropriate workup.

Synthesis of Diols and Related Materials (Table II). General Procedure. 4-(2-Hydroxymethylphenyl)-1-methyl-4-piperidinol (4, R = CH_3). Method A. A mixture prepared from dry THF (50 ml) and $LiAlH_4$ (0.91 g, 0.024 mol) was stirred under N_2 for 30 min and lactone **3** (R = CH_3, 1.3 g, 0.006 mol) in dry THF (25 ml) was added over a 30-min period. The mixture was refluxed for 3 h under N_2 and then hydrolyzed by addition of H_2O (1 ml) and 15% NaOH (1 ml) and finally with more H_2O (3 ml). The solution was filtered (sintered glass) and the precipitate was washed with THF (10 ml). The combined THF solution was dried ($MgSO_4$) and concentrated to give 1.3 g of **4** (mp 120–127 °C). Recrystallization of this product from $CHCl_3$–ligroin (bp 30–60 °C) gave pure **4**, mp 136–137 °C (86% yield).

Method B. The dilithio derivative prepared[13] from *o*-bromobenzyl alcohol (5.00 g, 0.0268 mol) was maintained at −20 °C while a solution of *N*-methyl-4-piperidone (4.20 g, 0.0369 mol) in dry hexane (15 ml) was added. The resulting slurry was maintained at −20 °C for 2 h and allowed to warm to room temperature (16 h). The resulting mixture was cooled (0 °C) and adjusted to pH 2 with 20% hydrochloric acid and was then extracted with ether. The acid solution was cooled (0 °C) and adjusted to pH 12 with aqueous NaOH. Extraction of the alkaline solution with ether gave 3.00 g of **4** (50.7% yield, mp 137–140 °C; mp 138.5–140 °C[10] from EtOH–benzene).

Other materials prepared by procedure B are described in Table II. Special comments follow.

Mercapto Alcohols 20 and 21. *o*-Bromobenzyl mercaptan[10,14] was prepared from *o*-bromobenzyl bromide, thiourea, and 95% EtOH [76% yield,[10] bp 42 °C (0.05 Torr)]. Lithium–halogen exchange was effected with *n*-butyllithium in the usual way[6] (1 h) but at −100 °C (liquid nitrogen–diethyl ether bath); ketone in hexane was added at −95 °C and after 1 h at this temperature the mixture was added to hydrochloric acid and processed as above.

Phenols 22–24. Reaction of *o*-bromophenol and *n*-butyllithium in THF was effected at −20 to −30 °C (3 h). The solutions were then cooled to −78 °C, ketone was added at −78 °C (3 h), and the resulting solution was allowed to warm to room temperature prior to addition to acid.

For 22 the acid solution was extracted with $CHCl_3$. The product was further characterized by its (0.005 mol) conversion into the cyclic carbonate by reaction with *n*-butyllithium (0.01 mol in hexane) in THF (20 ml) at 0 °C followed by addition of phosgene [0.0055 mol in benzene (3.5 ml)]. The resulting mixture was filtered and concentrated and the oil was chromatographed [silica gel using ether–ligroin (bp 30–60 °C) as eluent] to give an olefin (NMR) and solid (lower R_f, mp 77–80 °C). The solid was recrystallized from ligroin (bp 60–90 °C) to give the pure cyclic carbonate **17** (43% yield, mp 80–81 °C).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.28.

For 23 the reaction was carried out as described for **22.** The acidic solution was adjusted to pH 8–9 with aqueous bicarbonate and extracted with $CHCl_3$ in a continuous extractor for 3 days.

Diol 23 was converted into **4-(2′-hydroxyphenyl)-1-methyl-4-piperidinol dipropionate** by reaction with propionic anhydride (6 h, 32 °C). The crude dipropionate obtained in the usual way was distilled [short path, 140–145 °C (0.5 Torr); 79% yield] and the product solidified[10] (mp 67–77 °C dec).

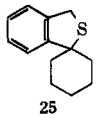
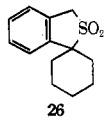
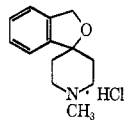
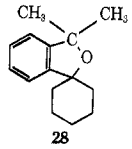
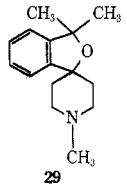
Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.83; H, 7.98; N, 4.17.

For 24 the procedure used was that described for **22.** The crude product (mp 105–107 °C) was mostly **24** but contained some 3-(2′-hydroxyphenyl)-2-tropene. The mixture was resolved by preparative TLC [600 g of basic alumina with ligroin (bp 30–60 °C)–EtOH as eluent]. The material with highest R_f was 3-(2′-hydroxyphenyl)-2-tropene (1.8% yield, mp 143–144 °C). Pure **24** was isolated in 20% yield.

For 15 (R = R^1 = CH_3) and 19. α,α-Dimethyl-2-bromobenzyl alcohol was prepared in 94% yield by reaction of methyl 2-bromobenzoate with CH_3MgI, bp 74–81 °C (0.09–0.07 Torr).

Synthesis of Spiro Piperidines (Tables I and III). 1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (5, R = CH_3). Method A. From Lactones. General Procedure. A mixture of lactone **3** (R = CH_3) (1.3 g, 0.006 mol) and freshly distilled boron trifluoride eth-

Table III. Conversion of Mercapto Alcohols or Diols to Spirobenzofurans 16 or Analogues[10]

Product	Conditions	Yield, %	Mp (or bp), °C
 25	**20** + 2 N H_2SO_4, 5 h, 100 °C	56	(90, 0.03 Torr)
 26	**25** + H_2O_2 in CH_3COOH	99	107–108[a]
 27	**21** + 4 N H_2SO_4, 18 h, 100 °C	*b*	>218 sublimes and dec
	**15** (R = H; R′ = CH_3) + formic acid, isolated as the hydrochloride	>60[c]	278–281[d]
5 (R = H; R′ = CH_3)	**15** (R = H; R^1 = CH_3) + 1 N H_2SO_4, 4 h, 100 °C	58[e]	78–80
5 ($R = CH_2C_6H_5$)	**15** (R = H; R^1 = $CH_2C_6H_5$) + 1 N H_2SO_4, 4 h, 100 °C	67	62–63[f]
 28	**22** + boron trifluoride etherate, 36 h, 32 °C in benzene	88	(56–58, 0.08 Torr)
 29	**23** + boron trifluoride etherate, 24 h, 32 °C in benzene	92	108[g]

[a] From $CHCl_3$–ligroin (bp 30–60 °C). [b] The crude free amine was obtained as an oil in nearly quantitative yield; however, it was difficult to purify. The hydrochloride was prepared from a $CHCl_3$ solution with ethereal HCl and was fractionally recrystallized from $CHCl_3$ with considerable loss of product. [c] Free base obtained as an oil. [d] From $CHCl_3$, lit. 281–282 °C. [e] Purified by preparative TLC (silica gel PF-254), ether eluent. [f] From solvent, previously reported as the hydrochloride. [g] From ligroin (bp 30–60 °C).

erate solution (25.5 g, 0.18 mol BF_3) was added slowly to a cold (5–10 °C) suspension of $LiAlH_4$ (0.91 g, 0.024 mol) in dry THF (100 ml). After addition was complete the stirred mixture was allowed to warm to room temperature (1 h) and was then heated at the reflux temperature under N_2 for 3 h. The mixture was cooled and hydrolyzed by addition of 25 ml of 5% hydrochloric acid and 25 ml of H_2O. The solution was concentrated (rotary evaporation) to ~50 ml and 25 ml of concentrated hydrochloric acid was added. The solution was refluxed for 6 h, then cooled and adjusted to pH 4 with concentrated aqueous NaOH. The mixture was extracted with ether. The acidic layer was cooled and adjusted to pH 9–10 with alkali; the resulting basic solution was extracted with five 100-ml portions of $CHCl_3$. The solid (1.5 g, mp 55–70 °C) obtained from the dried $CHCl_3$ extract was sublimed (60–65 °C, 0.02 Torr) to give 1.0 g (82% yield) of **5**[10] (R = CH_3, mp 78–80 °C)

1′-Methylspiro[isobenzofuran-1(3*H*),4′-tropane] (12) was prepared in a similar way from **11** (Table I) and was isolated pure from the crude product (mp 53–59 °C) by sublimation (50 °C, 0.02 Torr) in 18% yield[10] (mp 60–62 °C) as white crystals.

Method B. From Diols (Table II). General Procedure (Table III). A solution of 4-(2-hydroxymethylphenyl)-1-methyl-4-piperidinol (**4**, R = CH_3) (0.75 g, 3.39 mol) in 2 N sulfuric acid (20 ml) was stirred at the reflux temperature for 4 h. The mixture was then cooled, adjusted to pH 9 with alkali, and extracted with $CHCl_3$ (5 × 25 ml). The dried ($MgSO_4$) organic extract was concentrated to a yellow oil (0.69 g) which was purified by preparative TLC (silica gel PF-254 using anhydrous ether as eluent). The principal band was separated with MeOH to give 0.50 g of **5** (mp 69–70 °C). This product was sublimed (at 0.02 Torr) to give pure **5** (R = CH_3) (58% yield, mp 78–79 °C).

Other spirobenzofuran derivatives prepared[10] by similar procedures are presented in Table III; special comments follow.

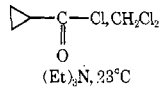
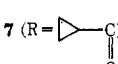
For 25. The product was extracted directly from the acid solution ($CHCl_3$) and was distilled. The product was also obtained in nearly quantitative yield from **20** (0.0023 mol) by using P_2S_5 (2 equiv) in CS_2 (100 ml) (48 h at 32 °C). The product was isolated from the filtered (6-cm bed of Celite) crude reaction mixture. Compound **25** was also characterized by its conversion to the sulfone **26**[10] (see Table III).

For 27. The crude oily product obtained from **21** (R = H; R^1 = CH_3) was dissolved in $CHCl_3$–ether and converted to the hydrochloride by addition of ethereal HCl. The crude hydrochloride was obtained in high yield; however, considerable loss occurred during fractional recrystallization from $CHCl_3$. The pure[10] hydrochloride (0.12 g from 2 g of crude base) (R = H; R^1 = CH_3) melted >218 °C with decomposition.

For 28. A solution of 1-*O*-(α,α-dimethyl-α-hydroxybenzyl)cyclohexanol (**19**, 2.0 g, 0.0085 mol) in benzene (100 ml) and boron trifluoride etherate (9.4 g, 0.128 mol) was stirred at room temperature for 36 h. The solution was washed with H_2O (100 ml) and aqueous bicarbonate (150 ml). Nearly pure **28** (1.80 g, 99% yield) obtained from the dried benzene was distilled to give pure **28** (1.7 g, 88% yield, see Table III). This product was also obtained in essentially quantitative yield by dehydration of **19** with P_2O_5 (1.5 equiv) in THF (24 h at 32 °C).

For 29. The procedure using **15** (R = R^1 = CH_3) and boron trifluoride etherate was quite similar to that used for **28**. Water (100 ml) and aqueous NaOH (to pH 14) was added and the mixture was ex-

Table IV. Akylation or Acylation of 6 and 9[10]

Substrate	Conditions	Product	Yield, %	Mp or (bp), °C
9	Styrene oxide, 100 °C, 2 h, no solvent	10 (R^1 = $CH_2CH(OH)C_6H_5$)	76	170–172[a]
9	$C_6H_5CH_2CH_2Br$ (2 equiv), K_2CO_3 (2.5 equiv) in 95% ethanol, 48-h reflux	10 (R^1 = $CH_2CH_2C_6H_5$)	72	103–105[b]
6	Styrene oxide, 105 °C, 2 h, no solvent	7 (R^1 = $CH_2CH(OH)C_6H_5$)	65	154.5–155.5[a]
6	$C_6H_5CH_2CH_2Br$, as above	7 (R^1 = $CH_2CH_2C_6H_5$)	45	96–98.5[c]
6	CH_2=$CHCH_2Br$, K_2CO_3 as above	7 (R^1 = CH_2CH=CH_2)	57	(100–105, 0.6 Torr)
6		7 (R^1 =	55	109–111[c,d]
7 (R = )	$LiAlH_4$ in THF	7 (R^1 = )	80	(112–115, 0.8 Torr)
6	CH_2=$CHCH_2CH_2Br$ + K_2CO_3, alcoholic	7 (R^1 = CH_2CH_2CH=CH_2)	71	(105–108, 0.1 Torr)

[a] From $CHCl_3$–ligroin (bp 30–60 °C). [b] Crude product sublimed (75–80 °C, 0.02 Torr). [c] By sublimation 60 °C (0.02 Torr). [d] Cyclopropanecarboxylic acid was removed at 55 °C (0.05 Torr) prior to sublimation.

tracted with $CHCl_3$. The crude product (mp 104 °C) obtained from the organic extracts was dissolved in petroleum ether, treated with Norite, and, subsequent to filtration, crystallized to give pure 29[10] (92% yield, Table III).

Demethylation Using Cyanogen Bromide. 1′-Cyanospiro-[isobenzofuran-1(3*H*),4′-piperidin]-3-one (8). A solution of lactone 3 (R = CH_3) (10.86 g, 0.05 mol) in $CHCl_3$ (100 ml) was added slowly to a stirred boiling solution of NCBr (10.59 g, 0.1 mol) in $CHCl_3$ (100 ml) under N_2 and the resulting solution was refluxed for 3 h. The resulting solution was extracted with 50 ml of 5% hydrochloric acid and then with 25 ml of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to give 10.1 g of solid, mp 179–181 °C. This product was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give 8.8 g (77% yield) of pure[10] 8 (mp 182–183 °C).

1′-Cyanospiro[isobenzofuran-1(3*H*),4′-piperidine] was obtained as a solid in quantitative yield; however, this material was used without purification for conversion into 6.

Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (9). A mixture of 8 (11.4 g, 0.05 mol) and 20% hydrochloric acid (200 ml) was stirred under N_2 at the reflux temperature for 6 h. The mixture was cooled (5 °C), the pH was adjusted to 9–10, and the mixture was extracted rapidly with five 200-ml portions of $CHCl_3$. The product obtained from the dried $CHCl_3$ was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give 8.4 g (83% yield) of pure 9 (mp 132–133 °C). This product was also obtained pure[10] in 76% yield by hydrolysis of 8 with alkali.

Spiro[isobenzofuran-1(3*H*),4′-piperidine] (6) was obtained (mp 84–86 °C from $CHCl_3$) from crude 1-cyanoisobenzofuran-1(3*H*),4′-piperidine pure[10] in 76% yield by acid hydrolysis and in 68% yield by basic hydrolysis, by procedures identical with that described above for 9.

Alkylation and Acylation Reactions (Products in Table IV). General Prodcedures and Comments. 1′-(β-Hydroxy-β-phenylethyl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one [10, R = $CH_2CH(OH)C_6H_5$]. A mixture of styrene oxide (1.2 g, 0.01 mol) and lactone 9 (2.0 g, 0.01 mol) was heated at 95–10 °C under a small air condenser for 3 h. The solid obtained when the mixture was cooled was washed with 10 ml of cold ligroin (bp 30–60 °C) and recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give pure[10] 10 (R = $C_6H_5CHOHCH_2$, mp 170–172 °C, 76% yield).

1′-(2-Phenylethyl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (10, R = $C_6H_5CH_2CH_2$). A solution of β-phenylethyl bromide (1.4 g, 0.0075 mol) in 95% EtOH (30 ml) was added slowly (12 h) to a boiling solution prepared from lactone 9 (1.0 g, 0.005 mol) in 95% EtOH (10 ml) under N_2. The resulting mixture was refluxed for an additional 36 h under N_2. The solution was concentrated (25 ml, rotary evaporator) and acidified (pH 2–3) with 10% hydrochloric acid and the solution was boiled for 30 min. The cooled solution (0 °C) was extracted with ether. The aqueous layer was cooled (0–5 °C) and a cold solution of NaOH (10%) was added to pH 9–10. This cold solution was rapidly extracted with five 100-ml portions of $CHCl_3$ and the combined product was obtained from the dried $CHCl_3$ extracts and was purified by two sublimations (75–80 °C, 0.02 Torr) to give pure[10] 10 (R = $C_6H_5CH_2CH_2$, mp 103–105 °C, 1.11 g, 72% yield). This product crystallized well from EtOH–H_2O.

Other alkylated products were prepared as described for 10 or by conventional procedures; yields and pertinent data are shown in Table IV.

Dehydration of Diols 15 (R = H, R^1 = CH_3), and 22 and 24. General Procedure. A stirred solution of 15 (R = H; R^1 = CH_3) (2.07 g, 0.01 mol) in 2 N sulfuric acid (50 ml) was refluxed for 4 h. The solution was cooled, saturated bicarbonate was added to pH 9, and the mixture was extracted with $CHCl_3$. The solid obtained from the dried $CHCl_3$ extract was recrystallized twice from $CHCl_3$–ligroin (bp 30–60 °C) to give pure[10] **4-(2′-hydroxyphenyl)-1-methyl-3-piperidine** (mp 152–153 °C, 50% yield).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.00; H, 8.10; N, 7.26.

4-(2′-Hydroxyphenyl)-2-tropene [mp 143–144 °C from $CHCl_3$–ligroin (bp 30–60 °C); 89% yield] and **2-(1′-cyclohexenyl)-phenol** (100% yield, analytical sample collected by GLC) were prepared in a similar manner from 24 and 22 respectively.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.39; H, 7.96; N, 6.25.

Preparation of 1′-Methylspiro[isobenzofuran-1(3*H*)-4′-piperidin]-3-imine (13). *o*-Bromobenzonitrile (5.00 g, 0.027 mol) in THF was converted into 2-lithiobenzonitrile at −78 °C (dry ice–acetone) as previously described[8]; *N*-methyl-4-piperidone (3.4 g, 0.03 mol) was added at such a rate that the temperature did not exceed −72 °C. Water (~100 ml) was added and the mixture was extracted rapidly with $CHCl_3$. The oil obtained from the dried ($MgSO_4$) $CHCl_3$ extract was distilled to give 4.2 g (72% yield of 13[10] [Table I, bp 137–142 °C (0.03 torr); mp 96–99 °C] from ligroin (bp 60–90 °C).

Registry No.—**2**, 59043-34-4; **3** (R = Me), 54595-70-9; **4** (R = Me), 59043-35-5; **5** (R = Me), 56657-95-5; **5** (R = CH_2Ph), 37663-43-7; **6**, 38309-60-3; **7** (R^1 = c-C_3H_5C=O), 59043-36-6; **7** (R^1 = $CH_2CH(OH)$-Ph), 59043-37-7; **7** (R^1 = CH_2CH_2Ph), 59043-38-8; **7** (R^1 = CH_2CH=CH_2), 59043-39-9; **7** (R^1 = c-$C_3H_5CH_2$), 56657-96-6; **7** (R^1 = CH_2CH_2CH=CH_2), 59043-40-2; **8**, 59043-41-3; **9**, 37663-46-0; **10** (R^1 = $CH_2CH(OH)Ph$), 59043-42-4; **10** (R^1 = CH_2CH_2Ph), 56657-84-2; **11**, 59043-43-5; **12**, 59043-44-6; **13**, 59043-45-7; **15** (R = H; R^1 = Me), 59043-35-5; **15** (R = H; R^1 = CH_2Ph), 56658-29-8; **15** (R = R^1 = CH_3), 59043-46-8; **17**, 59043-47-9; **19**, 59043-48-0; **20**, 59043-49-1; **21**, 59043-50-4; **22**, 59043-51-5; **23**, 59204-52-3; **24**, 59043-52-6; **25**, 28893-45-0; **26**, 59043-53-7; **27**, 59043-54-8; **28**, 59043-55-9; **29**, 59043-56-0; cyclohexanone, 108-94-1; spiro[isobenzofuran-1(3*H*),-1′-cyclohexan]-3-one, 5651-49-0; *N*-methylpiperidone, 1445-73-4; tropinone, 532-24-1; BrCN, 506-68-3; *o*-lithium benzonitrile, 59043-57-1; spiro[isobenzofuran-1,4′-piperidine]-1′-methyl HCl, 54596-08-6; styrene oxide, 96-09-3; $C_6H_5CH_2CH_2Br$, 103-63-9;

CH_2=$CHCH_2CH_2Br$, 5162-44-7; 4-(2'-hydroxyphenyl)-1-methyl-4-piperidinol dipropionate, 59043-58-2; 3-(2'-hydroxyphenyl)-2-tropene, 59043-59-3.

References and Notes

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Metathesis of 1-Alkene

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In the WCl_6/Bu_4Sn catalyzed metathesis of 1-alkene, the addition of esters, acetonitrile, phenylacetylene, dicyclopentadiene, and ethers raised the selectivity to the metathesis by depressing side reactions including double bond migration, and the products of the metathesis reaction were obtained in high yield. This is a very easy and effective process for the direct synthesis of the symmetric internal alkenes. In the metathesis of 1-octene catalyzed by the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system at 80 °C, the optimum range of the Bu_4Sn/WCl_6 ratio was 2–8 and that of the 1-octene/WCl_6 ratio 20–400. The cis:trans isomer ratio of the product olefin approached its equilibrium value at the end of the reaction.

The metathesis of 1-alkene gives an ethylene and a symmetric internal alkene as follows:

$$\begin{matrix} CH_2{=}CH{-}R \\ + \\ CH_2{=}CH{-}R \end{matrix} \rightleftarrows \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + \begin{matrix} HCR \\ \| \\ HCR \end{matrix}$$

It has been reported that this reaction is often accompanied by side reactions such as double bond migration and polymerization of alkenes[1-3] and that the yield of the metathesis products is low, except in a few cases.[4,5]

In this paper, we report that the WCl_6-CH_3COOR (R = Et, *n*-Pr, *n*-Bu, and *sec*-Bu)/Bu_4Sn and the WCl_6-CH_3CN/Bu_4Sn systems catalyzed the metathesis of 1-alkenes with high activity and high selectivity. This result appears to increase the merit of the metathesis reaction in synthetic chemistry.

Results and Discussion

Effects of Additives in the Metathesis of 1-Octene. In this study, tetrabutyltin[6] was employed as a cocatalyst because of the stability and the easiness to treat of the compound. Trichloroethylene[7] was used as a solvent, for it gave a good yield of the metathesis products without the formation of the undesirable Friedel–Crafts products in the metathesis of 2-heptene.

The WCl_6/Bu_4Sn catalyst system in combination with 1-octene afforded a mixture of alkenes ranging from C_2 to C_{14} in trichloroethylene at room temperature. At 80 °C, the amount of consumed 1-octene greatly increased, and the increase in the yield of alkenes ranging from C_9 to C_{14} was recognized. A polymerization reaction probably took place at the same time, since the amount of product alkenes was much less than that of the consumed 1-octene. The addition of *n*-propyl acetate to the reaction system suppressed the formation of alkenes ranging from C_9 to C_{13} and from C_3 to C_7, and the polymerization, but 7-tetradecene and ethylene were formed in high yield and in high selectivity. The addition of ethyl acetate, *n*-butyl acetate, and *sec*-butyl acetate also provided high yield of 7-tetradecene and high selectivity, respectively. The distribution of the alkenes ranging from C_8 to C_{14} was not influenced by the presence of air. In the WCl_6/Bu_4Sn catalyzed 1-octene metathesis, *cis*- and *trans*-2-octene, which are produced by the double bond migration of 1-octene, were detected by a capillary squalane column. Presumably alkenes ranging from C_2 to C_{14} were formed not only by the self-metathesis of 1- and 2-octene and by the cross-metathesis of 2-octene with 1-octene but also by the successive reactions of product alkenes such as the isomerization of 1-heptene into 2-heptene and the self- and the cross-metathesis of 2-heptene. The WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system reduced the amounts of *cis*- and *trans*-2-octene and the product alkenes ranging from C_9 to C_{13}. This fact indicates that the addition of *n*-propyl acetate suppresses the isomerization of 1-octene to 2-octene. These results are shown in Table I. Acetonitrile showed an excellent effect at the CH_3CN/WCl_6 ratio of 2, though the yield of 7-tetradecene decreased at the CH_3CN/WCl_6 ratio of 4. Phenylacetylene, dicyclopentadiene, ethyl ether, *n*-propyl ether, and tetrahydrofuran were also found to be comparatively effective additives. Water, hydrochloric acid, benzoic acid, tri-*n*-butylamine, tri-*n*-butylphosphine, and tetrahydrothiophene were not effective ones. In the presence of such compounds, the catalytic activity was hardly recognized at the additive/WCl_6 ratio of 1 and 4. Water, hydrochloric acid, and benzoic acid might destroy the catalyst. However, the addition of 1-propanol gave 11% 7-tetradecene at the equimolar amount to tungsten. Tri-*n*-butylamine, tri-*n*-butylphosphine, and tetrahydrothiophene induced yellow precipitations with a solution of tungsten hexachloride. Probably the stable acid–base tungsten complexes were formed.

Effects of Temperature and of the Amount of *n*-Propyl Acetate. The effects of temperature and of the CH_3COO-*n*-Pr/WCl_6 ratio on the yield and the selectivity were inves-