At lower temperatures (entries 4 and 6) oxidation of a 1,4-diol becomes significant, and modest yields of dione are obtained. However, considering the extended reaction time required to effect a minor conversion, this approach is not considered to be synthetically useful; the only reasonably attractive feature is that this route is catalytic. (3) The reaction is sensitive to the identity of the anion: the rate of cyclization is slower in the presence of nitrate and chloride than chloride alone. Lloyd observed a faster rate of oxidation in the presence of both nitrate and chloride.[4] This difference indicates that the palladium–diol complex undergoing dehydration (cyclization) has more chloride ligands than does the favored palladium–alcohol complex eventuating in carbonyl formation. (4) If copper is omitted (entry 9) the palladium precipitates out after a few minutes. Cyclization continues albeit at a slower rate; heterogeneous catalytic cyclization is well documented for palladium–aluminum alloys, though these are generally employed at significantly higher temperatures.[7] (5) 1,2-Dehydration was observed only with 1,3-butanediol and was slow. Pincol rearrangement products were not observed for any 1,2-diol. (6) The role of Pd(II) in the cyclization is considered to be simply that of a Lewis acid.

Experimental Section

Reactions under Oxygen. Oxidations were carried out in a standard, low-pressure catalytic apparatus (Parr Instrument Co., Model 3911). In typical run a 500-ml glass reactor vessel was charged with 30.0 g of diol along with the desired amounts of catalyst, and the system was sealed, purged three times with oxygen, then pressurized to 60 psig oxygen pressure and rapidly brought to the desired temperature by means of a heating mantle. The temperature was established by standardizing the mantle and variac without pressurizing the system. After the desired time had passed, the reactor was cooled and the contents were collected for analysis.

Product separations and yields were determined by distillation and/or gas chromatography. Product identities were determined by IR, NMR, and mass spectral data.

Acknowledgment. We would like to thank the Western Kentucky University Faculty Research Program for their generous support.

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A Novel Reaction of Some Fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols in 97% Formic Acid

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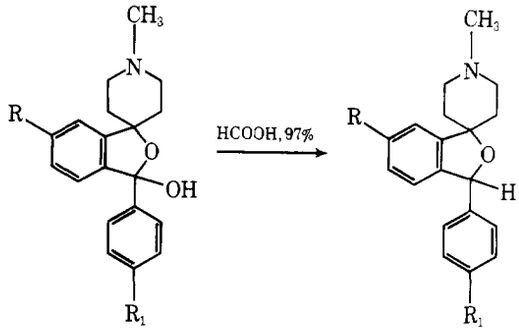
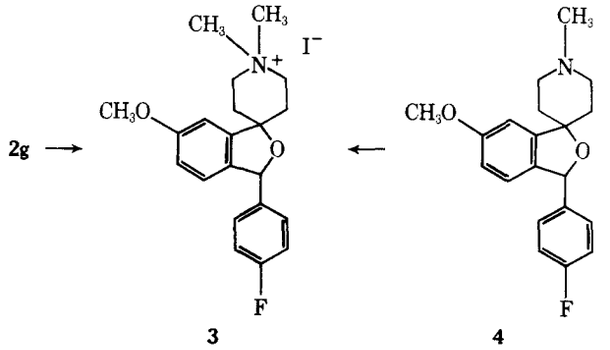
The continued interest in these laboratories in spiro[isobenzofuran-1(3*H*),4′-piperidines] as potential CNS agents[1] prompted an investigation of the recently published[2] reduction in 97% formic acid of 1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (**1a**) to 1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (**2a**). We have duplicated the published[2] yield of **2a** using identical procedures. Furthermore, we have found that the 6-chloro- and 3-(4-chlorophenyl) analogues of **1a** are reduced cleanly under these conditions to the corresponding analogues of **2a** in recrystallized yields of 85 and 82%, respectively. TLC and NMR showed no evidence of anomalous by-products in either case. However, the reduction of the 3-(4-fluorophenyl) analogue (**1b**)[2] or the 6-fluoro analogue (**1c**) led not only to the corresponding fluorospiro[isobenzofuran-1(3*H*),4′-piperidines] (**2b** and **2d**, in 71 and 36% yields, respectively) but also led to the hydroxy analogues (**2c** and **2e**, in 14 and 41% yields, respectively). Furthermore, both **2f** and **2g** were isolated (in 42 and 23% yields, respectively) from the reduction of the difluoro analogue (**1d**).



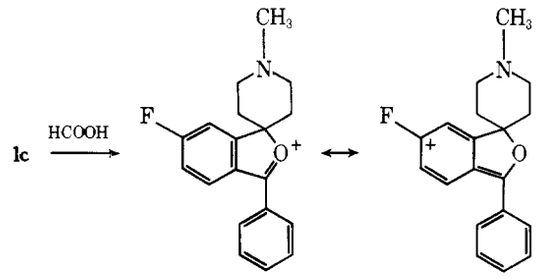
1a, R = R′ = H
b, R = H; R′ = F
c, R = F; R′ = H
d, R = R′ = F

2a, R = R′ = H
b, R = H; R′ = F
c, R = H; R′ = OH
d, R = F; R′ = H
e, R = OH; R′ = H
f, R = R′ = F
g, R = OH; R′ = F

The structures of **2b–f** were proved by comparison of melting points and infrared and ^{1}H NMR spectra with samples obtained in alternate unambiguous syntheses.[1] The orientation of the hydroxy and fluoro substituents of **2g** was demonstrated by conversion to the methoxy methiodide (**3**). This was shown to be identical with the methiodide obtained from 4 that had been prepared unambiguously.[1]



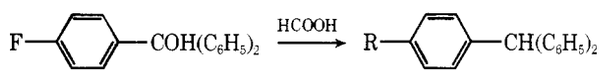
In the case of the reduction of **1c** to **2d** and **2e**, **2d** could not



5

be converted to **2e** by further refluxing in formic acid. This observation suggested that the aromatic fluorine is activated for substitution by the stabilized carbonium ion **5** that is subsequently reduced by formate.[3] The substitution that is observed could result from the capture of water by **5** and the loss of fluoride (or HF). The failure to observe any hydroxylated by-products in the case of the chloro analogues is apparently a manifestation of the greater mobility of fluorine over chlorine in aromatic substitution reactions, particularly in a polar, protic solvent such as formic acid.[4]

The possible intermediacy of **5** in the reduction reactions suggested that the reduction of 4-fluorotriphenylmethanol (**6**) in 97% formic acid would be instructive, as the formation of a stable carbonium ion would also be anticipated.[3,5] Bowden and Watkins[6] studied the reactivity of **6** with 98% formic acid by means of evolved carbon dioxide but did not isolate any products. Taft et al.[7] reported the preparation of 4-fluorotriphenylmethane (**7a**) by the formic acid–sodium formate



6 **7a**, R = F
b, R = OH

reduction of **6**; no product other than **7a** was isolated. Our investigation, however, revealed that 4-hydroxytriphenylmethane (**7b**) is formed in 13% yield together with 4-fluorotriphenylmethane (**7a**, 79% yield) in the reduction of **6** with either formic acid alone or formic acid–sodium formate.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. ^{1}H NMR spectra ($CDCl_3$/Me_4Si) were recorded on a JEOLCO C60HL and the ^{13}C NMR spectra were obtained on a JEOLCO JNM-FX 60 operating at 15 MHz in the Fourier transform mode. The carbon shifts indicated for **7a** and **7b**[10] are from a $CDCl_3$ solution and are in parts per million downfield from Me_4Si. Formic acid (97+%) was obtained from the Aldrich Chemical Co. and was used without further purification. 6-Fluoro-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (**8**) and 3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (**1b**) were synthesized according to Marxer et al.[2]

6-Fluoro-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (1c). Phenylmagnesium bromide (0.12 mol) was refluxed for 2 h with 0.081 mol of **8**[2] in 425 ml of dry THF. The reaction mixture was chilled and the insoluble bromomagnesium salt was filtered and washed well with dry Et_2O under anhydrous conditions. This salt was hydrolyzed in aqueous NH_4Cl and the product filtered, washed with water, and recrystallized from EtOAc to give 16.2 g (64%) of **1c**, mp 185–187 °C: NMR δ 1.8–3.1 [m, 11 H, piperidine ring H and CH_3 (s at 2.30)], 5.5 (s, broad, 1 H, OH), 7.0–7.8 (m, 6 H, H-4,5,7 and H-3,4,5 of 3-phenyl), 7.9–8.2 (m, 2 H, H-2,6 of 3-phenyl).

Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.82; H, 6.43; N, 4.47. Found: C, 72.72; H, 6.44; N, 4.52.

6-Fluoro-3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol (1d). In a manner identical with the synthesis of **1c**, **8**[2] was reacted with 4-fluorophenylmagnesium bromide to give, after recrystallization from benzene/THF, 77% of **1d**, mp 179–180.5 °C: NMR δ 1.9–2.9 [m, 11 H, piperidine ring H and CH_3 (s at 2.36)], 4.7 (s, broad, 1 H, OH), 7.1–7.6 (m, 5 H, H-4,5,7 and H-3,5 of 3-phenyl), 7.9–8.2 (m, 2 H, H-2,6 of 3-phenyl).

Anal. Calcd for $C_{19}H_{19}F_2NO_2$: C, 68.87; H, 5.78; N, 4.23. Found: C, 69.10; H, 5.89; N, 4.06.

General Procedure for Formic Acid Reduction of Fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols. The method employed was similar to that of Marxer et al.,[2] involving a 2-h reflux of the fluorospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ol in 97% formic acid (ca. 2.5 ml/mmol) followed by the concentration of the reaction mixture under reduced pressure. The residue was distributed between $CHCl_3$ and water, the aqueous phase was made basic with 50% NaOH, and the layers were shaken again. The organic phase was then withdrawn, dried ($MgSO_4$), and concentrated under reduced pressure to give a residue that was worked up in the indicated manner.

3-(4-Fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2b) and 3-(4-Hydroxyphenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2c). On a run of 0.123 mol of **1b**,[2] concentration of the chloroform phase gave a crystalline solid that was treated with hot cyclohexane. The solution was filtered while hot, then allowed to cool. The cyclohexane insoluble material was recrystallized from toluene to give 14% of **2c**, while 71% of **2b** crystallized from the cyclohexane. These two compounds were identical by IR, NMR, and TLC with authentic samples that had been synthesized by unambiguous routes.[1] The melting point of **2c** was 272 °C dec (lit.[1] mp 273–276 °C dec) and **2b** had mp 124–125 °C (lit.[1] mp 126–127 °C).

6-Fluoro-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2d) and 6-Hydroxy-1′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2e). On a run of 0.05 mol of **1c**, treatment of the gummy residue from the chloroform phase with hot hexane gave 41% of **2e** as an insoluble sediment. Thirty-six percent of **2d** crystallized from the hexane. As above, both **2e** and **2d** were spectrally and chromatographically identical with authentic samples and had mp 200–202 °C dec and 123–124 °C, respectively (lit.[1] mp 207–212 and 127–129 °C).

6-Fluoro-3-(4-fluorophenyl)-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2f) and 3-(4-Fluorophenyl)-6-hydroxy-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (2g). On reduction of 0.03 mol of **1d**, treatment of the concentrated reaction residue with chloroform gave a gummy precipitate that dissolved in 10% NaOH. An emulsion developed when this solution was shaken with chloroform, but cleared when the pH was adjusted to ca. 11. The aqueous phase was separated and adjusted to pH 4–5, precipitating a white solid. This was filtered and combined with a little additional material (identical by TLC) that precipitated from the chloroform over ca. 1 h. Recrystallization from EtOAc/hexane gave 23% of **2g**, mp 219–221 °C dec: NMR δ 1.9–3.2 [m, 11 H, piperidine ring H and CH_3 (s at 2.45)], 6.36 (s, 1 H, H-3), 7.0–7.8 (m, 8 H, aromatic H and OH).

Anal. Calcd for $C_{19}H_{20}FNO_2$: C, 72.82; H, 6.43; N, 4.47; F, 6.06. Found: C, 73.00; H, 6.63; N, 4.36; F, 6.01.

Evaporation of the chloroform phase gave 42% of **2f** as a gummy solid which, after recrystallization from cyclohexane, was spectrally and chromatographically identical with an authentic sample and had mp 131–133 °C (lit.[1] mp 134–135 °C).

1′,1′-Dimethyl-3-(4-fluorophenyl)-6-methoxyspiro[isobenzofuran-1(3*H*),4′-piperidinium] Iodide (3). A solution of **2g** (0.2 g, 0.64 mmol) in DMF (5 ml) was treated first with NaH (0.03 g, 1.25 mmol), warmed to 50 °C, and then treated with MeI (0.12 ml, 1.9 mmol). The addition of water (10 ml) precipitated the methiodide, which was recrystallized from *i*-PrOH/MeOH, mp 301 °C dec: NMR (Me_2SO) δ 1.8–3.0 (m, 4 H, H-3′,5′), 3.4–4.9 (m, 10 H, H-2′,6′ and NCH_3's), 3.98 (s, 3 H, OCH_3), 6.42 (s, 1 H, H-3), 7.1–7.8 (m, 7 H, aromatic H).

Anal. Calcd for $C_{21}H_{25}FINO_2$: C, 53.74; H, 5.37; N, 2.99; I, 27.04. Found: C, 53.58; H, 5.39; N, 2.90; I, 26.88.

Treatment of a solution of 3-(4-fluorophenyl)-6-methoxy-1′-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] hydrobromide[1] (**4**, 0.15 g, 0.46 mmol) in DMF (5 ml) with $NaHCO_3$ (0.3 g, 3.6 mmol) and then MeI (0.04 ml, 0.6 mmol) gave an identical product (melting point, NMR) upon workup as above.

Formic Acid Reduction of 4-Fluorotriphenylmethanol (6). A solution of **6** (4.0 g, 0.014 mol) in 50 ml of 97% formic acid was refluxed for 2 h. The reaction mixture was then cooled and extracted with hexane. The formic acid was concentrated under reduced pressure and the residue worked up as in the previous examples. Concentration of the chloroform phase gave 0.46 g (13%) of 4-hydroxytriphenylmethane (**7b**) as an orange solid. One recrystallization from hexane gave material of mp 109–111 °C (lit.[8] mp 109–110 °C): NMR δ 5.0 (s, broad, 1 H, OH), 5.70 (s, 1 H, CH), 6.92–7.08 (AB d, 2 H, J = 11.0 Hz, *p*-hydroxyphenyl H), 7.20–7.36 (AB d, partially obscured, 2 H, J = 11.0 Hz, *p*-hydroxyphenyl H), 7.2–7.7 (m, 10 H, aromatic H).[10]

Concentration of the hexane extracts gave 2.9 g (79%) of slightly yellow 4-fluorotriphenylmethane (**7a**). One recrystallization from methanol gave colorless crystals, mp 62–63 °C (lit.[9] mp 40–42 °C). Because the melting point difference was great, the sample was analyzed and its NMR spectrum recorded: NMR δ 5.50 (s, 1 H, CH), 6.7–7.3 (m, 14 H, aromatic H).[10]

Anal. Calcd for $C_{19}H_{15}F$: C, 87.00; H, 5.76; F, 7.24. Found: C, 86.83; H, 5.86; F, 7.13.

Similar results were obtained when the formic acid contained 0.1 M sodium formate.

Acknowledgment. The author is indebted to Mr. David Clare for the ^1H NMR measurements and to Mr. Marc Agnew for the ^{13}C NMR measurement and interpretation of **7a** and **7b**. Thanks are also due Mrs. Kathleen Huppert for assistance in preparation of this manuscript.

Registry No.—**1b**, 54595-78-7; **1c**, 60582-06-1; **1d**, 60582-07-2; **2b**, 59142-51-7; **2c**, 59143-29-2; **2d**, 60081-30-3; **2e**, 59143-25-8; **2f**, 59142-50-6; **2g**, 60582-08-3; **3**, 60582-09-4; **4**, 60081-31-4; **6**, 427-39-4; **7a**, 437-23-0; **7b**, 791-92-4; **8**, 54595-73-2; phenyl bromide, 108-86-1; 4-fluorophenyl bromide, 460-00-4.

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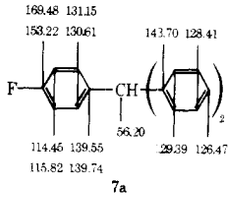
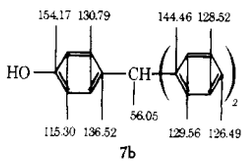
(10) The structures of **7a** and **7b** were confirmed by ^{13}C NMR. The carbon shifts are delineated below.



7a



7b

Enolate Amination with *O*-Mesitylenesulfonylhydroxylamine[1]

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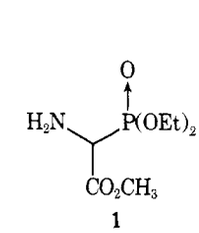
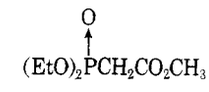
Received June 24, 1976

We wish to report the use of enolate amination to achieve a short, simple preparation of a key intermediate for cephalosporin synthesis, methyl α-aminodiethylphosphonoacetate (**1**).[3] Reaction of methyl diethylphosphonoacetate with sodium hydride, followed by the addition of *O*-mesitylenesulfonylhydroxylamine,[4] afforded **1** in 39–47% yield. The major impurity was the neutral **2**, which was conveniently removed by extraction of **1** into aqueous *p*-toluenesulfonic acid. By way of contrast, the previous synthesis of **1** goes in 18–21% yield, and it involves five steps and a chromatography.[3] This method of enolate amination is similar to an approach which has been described by Yamada for the synthesis of α-amino acids.[5]

We have extended the utility of the intermediate **1** to the preparation of a cephem with a methylthio substituent in the 6 position. Condensation of **1** with carbon disulfide in aqueous K_2HPO_4, followed by the addition of methyl iodide, gave the dithiocarbamate **4** in 25% yield. By analogy to the Merck report,[6] the reaction of **4** with chloroacetone in acetone containing K_2CO_3 gave the expected thiazine **5** in 81% yield. When a mixture of **5** and diphenylketene was heated under N_2 at 110 °C for a total of 4 h, there was obtained after preparative TLC workup the β-lactam **6**.



1



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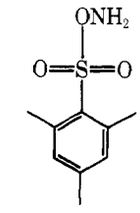

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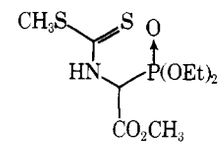

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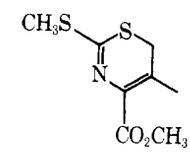

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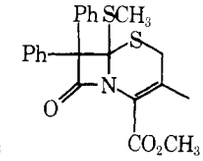

6

We were unsuccessful in our attempts to add azidoketene to the thiazine **5** under conditions which we had used for other imines.[7] The unreactivity of **5** toward azidoketene is consistent with the results from our model studies, and it probably stems in large part from the conjugation of the dithioimine unit with a double bond.

Experimental Section

IR spectra are in $CHCl_3$ and NMR spectra are in $CDCl_3$.

Methyl α-Aminodiethylphosphonoacetate (1). To a suspension of 210 mg of sodium hydride (57% mineral oil dispersion) in 15 ml of dimethoxyethane (DME) was added dropwise 1.07 g (5 mmol) of methyl diethylphosphonoacetate (**2**). After cessation of gas evolution there was added dropwise over a 15-min period a solution of ca. 1.05 g (4.9 mmol) of *O*-mesitylenesulfonylhydroxylamine (**3**)[4,8] (see *Caution*) in 5 ml of DME (temperature held below 30 °C). After stirring for 30 min the mixture was filtered and the filtrate was evaporated in vacuo to give a crude product whose main contaminant was **2**. The crude product was dissolved in $CHCl_3$ and was extracted twice with aqueous *p*-toluenesulfonic acid. The aqueous phase was extracted with $CHCl_3$, basified with K_2HPO_4, and thoroughly extracted with $CHCl_3$. After drying over Na_2SO_4 and removal of solvent there was obtained 530 mg (47%) of TLC pure **1**, whose IR and NMR spectra were in accord with the published values.[3]

Caution: We experienced a mild explosion in attempting to dry 4.5 g of **3** *at room temperature under vacuum.*[8] *Subsequent to this explosion we dispensed with the vacuum drying step of ref 8 and in its place we substituted a routine in which the wet* **3** *obtained according to ref 8 was dissolved in DME and the solution was dried over 4A molecular sieves for ca. 1 h.*

Methyl α-(*S*-Methyldithiocarbonyl)aminodiethylphosphonoacetate (4). A mixture of 225 mg (1 mmol) of **1** 100 mg of carbon disulfide (excess), 87 mg (1 mmol) of dipotassium hydrogen phosphate, and 7 ml of water was stirred at room temperature for 6 h. Methyl iodide (142 mg, 1 mmol) was added and the mixture was stirred for an additional 2 h. The mixture was extracted with an equal volume of diethyl ether. The aqueous layer was treated with 100 mg of carbon disulfide and 40 mg of K_2HPO_4, stirred for 5 h, treated with 142 mg of methyl iodide, stirred for 2 h, and extracted with an equal volume of diethyl ether. The combined ether extract was dried (Na_2SO_4) and concentrated to a gum. A crystalline product, mp 91–92 °C, was obtained from diethyl ether–hexane (80 mg, 25%): IR 1746 cm^{-1}; NMR δ 1.34 (t, J = 7 Hz, CH_2CH_3), 2.64 (s, SCH_3), 3.82 (s, OCH_3), 4.22 (m, $POCH_2CH_3$), 6 (d of d, J_{HP} = 21.5, $J_{NH} \sim$ 7.5 Hz, NHCHP), 7.95 (broad, NH); *m/e* (70 eV) 315 (M^+). Anal. Calcd for $C_9H_{18}NPO_5S_2$: C, 34.28; H, 5.75; N, 4.44. Found: C, 34.41; H, 5.85; N, 4.35.

Synthesis of Methyl 5-Methyl-2-methylthio-6*H*-1,3-thiazine-4-carboxylate (5) and Its Conversion to Methyl 3-Methyl-6-methylthio-7,7-diphenylceph-3-em-4-carboxylate (6). Di-