Synthesis and Reactions of 4-Isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones

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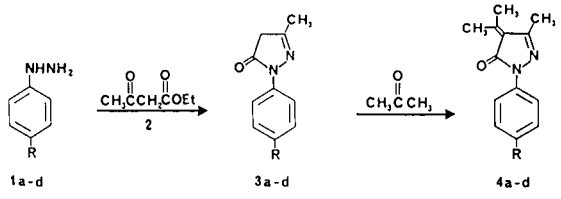
Received July 16, 1986

The reactions of 4-isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones **4a-d** were investigated under a variety of conditions. In the presence of thiols or piperidine, **4a-d** failed to yield conjugate addition products, presumably due to the steric bulk provided by the two methyl substituents of the isopropylidene side chain. Reaction of **4a-d** with hydrazine derivatives gave the 1-aryl-3-methyl-2-pyrazolin-5-ones **3a-d** and isopropylhydrazones. Treatment of **4a** with potassium cyanide yielded a stable conjugate addition product which exists as a mixture of tautomers in different solvents. Also, oxidation of **4a** with hydrogen peroxide gave a spiroepoxide **22**, while *m*-chloroperbenzoic acid oxidation afforded both the spiroepoxide **22**, and a small quantity of a hydroxyspiroepoxide **23**.

J. Heterocyclic Chem., **24**, 149 (1987).

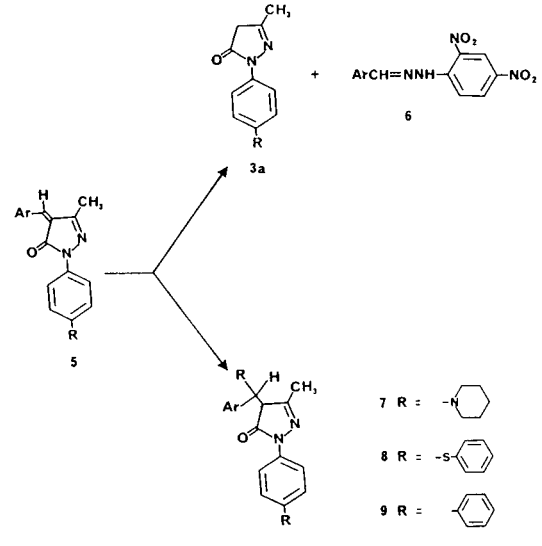
The synthesis of 4-alkylidene- and 4-arylidene-1-aryl-3-methyl-2-pyrazolin-5-ones has been the subject of numerous publications over the past several decades [1]. However, while a great number of compounds of this structural type have been prepared, there are relatively few reports describing the chemical reactivity of these compounds, particularly the 4-alkylidene derivatives. As part of a research program to obtain structurally novel central nervous system depressants, we synthesized several 4-isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones **4a-d**. In addition to evaluating these compounds pharmacologically, we also investigated the reactions of these compounds under a variety of conditions.

The 4-isopropylidene derivatives **4a-d** were synthesized by condensation of 1-aryl-3-methyl-2-pyrazolin-5-ones **3a-d** with acetone as described by Westoo (Scheme 1) [2]. The pyrazolin-5-one starting materials **3a-d** were prepared by treatment of the appropriate 4-substituted phenylhydrazines **1a-d** with ethyl acetoacetate (**2**) as originally reported by Knorr [3].

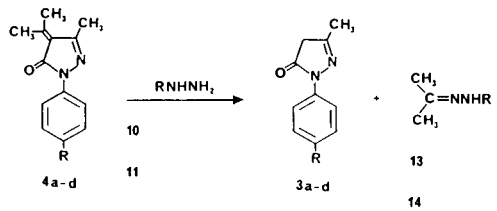


Scheme 1

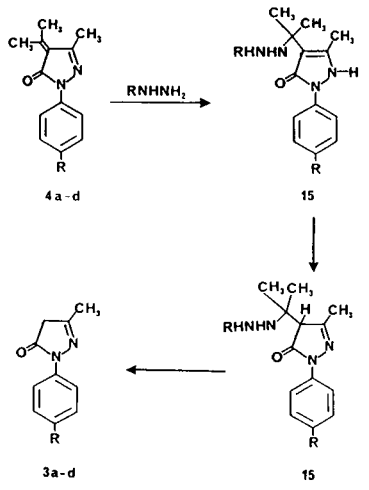
Ruhmann [4] and Mustafa *et al.* [5] investigated the reactions of several 4-arylidene-1-phenyl-3-methyl-2-pyrazolin-2-ones **5** - compounds closely related in structure to isopropylidene **4a-d** - in the presence of a variety of nucleophilic species. They found that when treated with 2,4-dinitrophenylhydrazine, these compounds gave the pyrazolin-5-one **3a** and hydrazones **6** (Scheme 2). Also, when allowed to react with piperidine, thiophenol or phenyl magnesium bromide, the 4-arylidene derivatives underwent conjugate addition reactions typical of α,β-unsaturated carbonyl-containing compounds to give **7**, **8**, and **9**, respectively (Scheme 2). These observations prompted us to explore the reactivity of isopropylidenes **4a-d** under similar conditions. Reaction of isopropylidenes **4a-d** with 2,4-dinitrophenylhydrazine (**10**) or semicarbazide (**11**) resulted in formation of pyrazolones **3a-d** and the corresponding hydrazones **13** and **14** (Scheme 3). These findings are directly analogous to those reported by Mustafa with the 4-arylidene-1-phenyl-3-methyl-2-pyrazolin-5-ones. These reactions appear to proceed by a stepwise mechanism involving first conjugate addition of the amine or hydrazine derivative to give intermediates of general structure **15**. The addition is then followed by tautomerization and elimination to give the intact pyrazolin-5-one heterocycles **3a-d** and the hydrazones **13** and **14** (Scheme 4).



Scheme 2

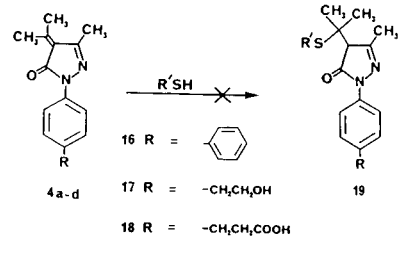


Scheme 3



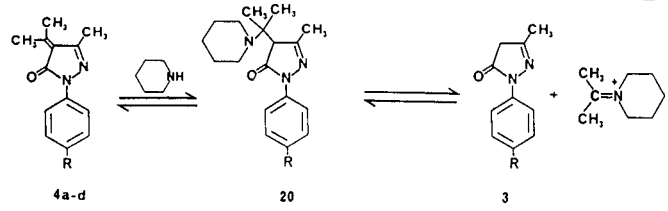
Scheme 4

Treatment of isopropylidenes **4a-d** with one equivalent of a thiol derivative such as thiophenol **(16)**, 2-mercaptoethanol **(17)** or 3-mercaptopropionic acid **(18)** in an organic solvent or mixture of a protic organic solvent and water did not result in the formation of conjugate addition products **19** (Scheme 5); only unreacted **4a-d** were recovered from these reaction mixtures. The observation that the structurally related 4-arylidenes readily undergo addition in the presence of thiols suggests that the methyl substituents present at the reaction site of isopropylidenes **4a-d** may provide sufficient steric bulk to hinder facile addition of the thiol nucleophiles. Alternatively, it is possible that conjugate addition can occur with a thiol, but that the steric interaction between the 3-methyl substituent and the bulky 4-substituent of the addition product **19** may destabilize this adduct, favoring the reverse reaction.



Scheme 5

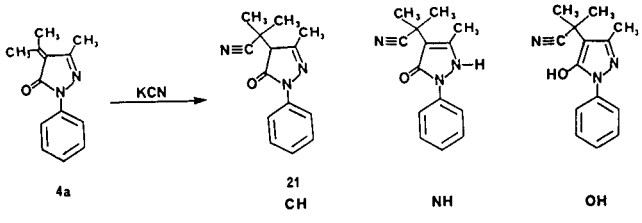
Reaction of **4a-d** with one equivalent of piperidine in benzene, using the method of Mustafa *et al.*, also did not result in formation of the expected addition products **20** (Scheme 6). Monitoring of the reaction of **4a** with piperidine by reverse-phase liquid chromatography revealed that a small quantity of the pyrazolin-5-one **3a** had formed. This observation was confirmed by chromatographic workup of the reaction mixture which resulted in the recovery of the starting isopropylidene **4a** (approximately 80%) and a small quantity of the pyrazolin-5-one **3a** (< 10%). The isolation of **3a** suggests that some addition product **20a** may form, but that this product is unstable, eliminating to give either the starting isopropylidene **4a** or the pyrazolin-5-one **3a** (Scheme 6). The instability of the addition product **20a** can again be rationalized on the basis of steric interactions between the 3-methyl substituent and the bulky tetrahedral substituent at the 4-position. Additionally the methyl groups present at the reaction site of **4a** may slow addition of the piperidine nucleophile by a steric mechanism. Further evidence in support of these hypotheses is provided by the observation that when the reaction was repeated with three equivalents of piperidine, the pyrazolin-5-one **3a** was formed in greater yield (15 to 20%).



Scheme 6

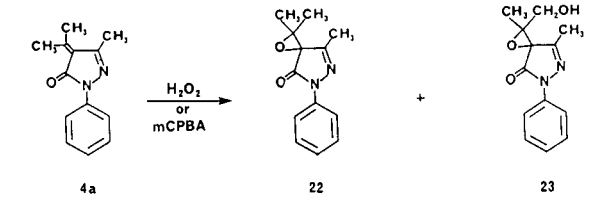
The reaction of isopropylidene **4a** with potassium cyanide in aqueous ethanol did yield a stable conjugate addition product **21** (Scheme 7). The proton nuclear magnetic resonance spectrum of **21** in deuteriochloroform is relatively complex with a multiplet at δ 7.1 to 7.8 (5H) and apparent singlets at δ 3.32, δ 2.35, δ 2.28, δ 1.81, δ 1.68, and δ 1.29. These spectral data suggest that **21** may exist as a mixture of the CH, NH and possibly OH tautomers in deuteriochloroform. On the other hand, the proton spectrum of **21** in dimethylsulfoxide-d_6 contains only a multiplet at δ 7.1 to 7.7 (5H) and singlets at δ 2.33 (3H) and δ 1.69 (6H) indicating that, in this solvent, **21** exists as a single tautomer. These observations prompted us to study the tautomeric nature of **21** in both deuteriochloroform and dimethylsulfoxide-d_6 by comparing its proton spectra and infrared spectra in these solvents to the spectra of pyrazolin-5-ones **3a-d**. The proton spectra of **3a-d** in deuteriochloroform have multiplets in the δ 7.0 to 8.2 region (aromatic protons) and singlets at approximately δ 3.4 (2H) and δ 2.2 (3H), demonstrating that these compounds exist solely in the CH tautomeric form in this sol-

vent. The carbonyl moieties for all of these pyrazolin-5-ones in the CH tautomeric form (deuteriochloroform) absorb strongly at approximately 1710 cm^{-1} in the infrared spectrum. The proton spectra of **3a-d** in dimethylsulfoxide-d_6 reveal that these compounds exist almost completely in the NH tautomeric form with multiplets in the δ 6.9 to 8.2 region (aromatic protons) and singlets at approximately δ 5.3 (1H) and δ 2.1 (3H). The carbonyl moieties for the NH tautomers of **3a-d** provide an intense absorption at approximately 1655 cm^{-1} in the infrared spectra. The difference in carbonyl absorptions for the CH (1710 cm^{-1}) and NH (1655 cm^{-1}) tautomers of **3a-d** is analogous to differences typically observed for the carbonyl moieties present in unconjugated and conjugated cyclic esters and amides [6]. By using the difference in the carbonyl absorption for a CH and NH tautomer, as well as proton nuclear magnetic resonance spectral data, we were able to determine the tautomeric composition of the nitrile **21** in both deuteriochloroform and dimethylsulfoxide-d_6. The single tautomer observed by proton spectroscopy for **21** in dimethylsulfoxide-d_6 displays an intense carbonyl absorption at 1650 cm^{-1}, demonstrating that the NH tautomer of **21** is preferred in this solvent. Also, the tautomeric mixture detected by proton spectroscopy for **21** in deuteriochloroform has infrared absorptions at 1710 cm^{-1} and 1650 cm^{-1}, indicating that both the CH and NH tautomers of **21** are present in this solvent. Furthermore, integration of the proton spectrum of **21** in deuteriochloroform reveals that the ratio of CH to NH tautomer in this solvent is 63% to 37% (determined from the integrals of the aromatic protons at δ 7.1 to 7.8 and the 4-proton at δ 3.32). None of the OH tautomer was detected in deuteriochloroform as indicated by the integrals in the nuclear magnetic resonance spectrum, as well as the lack of an OH absorption in the infrared spectrum.

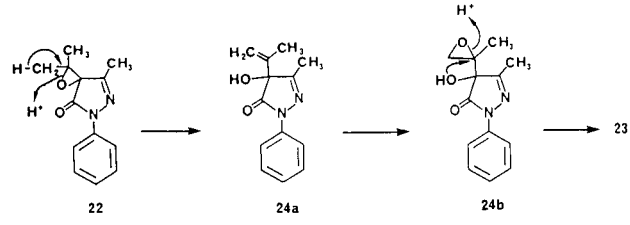


Scheme 7

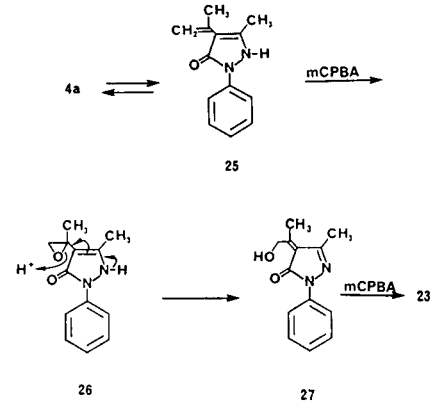
Oxidation of **4a** with 30% hydrogen peroxide in glacial acetic acid resulted in the formation of the expected spiroepoxide derivative **22** (Scheme 8). When **4a** was treated with 1.1 equivalents of *m*-chloroperbenzoic acid in benzene, the spiroepoxide **22** again formed as the major product (80%), along with a small quantity (<5%) of the hydroxy spiroepoxide **23** (Scheme 8). The structure of **23** was confirmed by elemental analysis as well as infrared and proton nuclear magnetic resonance spectroscopy; the proton spectrum of **23** contains a doublet at δ 4.18 (2H) and a triplet at δ 3.1 (1H) which exchanges in deuterium oxide demonstrating the presence of the primary alcohol functionality. Originally it was thought that **23** might form from the spiroepoxide **22** by a mechanism involving ring opening to the hydroxy alkene **24**, followed by oxidation (Scheme 9). If this hypothesis is correct, it should be possible to convert **22** to **23** under the original reaction conditions. However, when epoxide **22** was treated with *m*-chloroperbenzoic acid or mixtures of *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid for up to 48 hours, none of the hydroxy spiroepoxide **23** formed (liquid chromatographic evaluation); unreacted epoxide **22** was recovered quantitatively from these reaction mixtures. Therefore, it appears that **23** may form directly from the starting isopropylidene **4a**, perhaps by a mechanism involving tautomerization to the diene **25**, followed by an oxidation sequence (Scheme 10).



Scheme 8



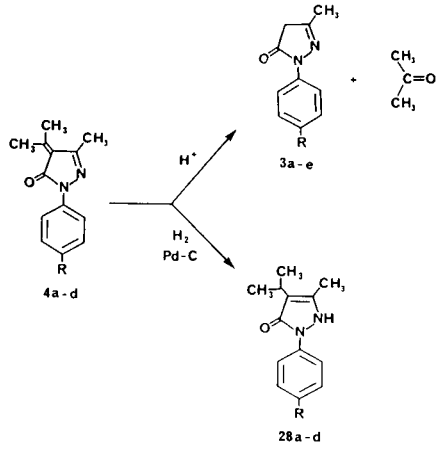
Scheme 9



Scheme 10

In addition to the reactions described above, the behavior of isopropylidenes **4a-d** was also investigated under a variety of other conditions. In the presence of

aqueous acid, **4a-d** undergo a retro-aldol reaction to give the intact 1-aryl-3-methyl-2-pyrazolin-5-ones **3a-d** and acetone (Scheme 11). When 48% hydrobromic acid is used as the acid, isopropylidene **4c** also undergoes to demethylation to give **3e**. When subjected to catalytic hydrogenation, as described by Zivkovic *et al.*, **4a-d** are converted to the corresponding 4-isopropyl derivatives **28a-d** [7]. During the course of this reaction, the nitro group of **4d** is also reduced to the amine **28d**. (Scheme 11).



Scheme 11

At the present time we continue to investigate the reactivity of the 4-isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones **4a-d**. We are also exploring reactions to convert the nitrile **21** to bicyclic heterocycles, and the epoxide **22** to novel 6-membered heterocycles. The results of these studies will be the subject of future publications.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded with a Bechman 4230 spectrophotometer and ^{1}H nmr were recorded on a Varian T-60A spectrometer with tetramethylsilane as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia and are with 0.4 of the theoretical percentages. Reverse-phase hplc analyses were carried out with a Waters Model 6000A Liquid Chromatograph equipped with a Zorbax ODS C-18 column (4.6 mm x 15 cm) and a Waters Model 440 absorbance detector set at 254 nm, using a 80% methanol-water eluting solvent system. Common reagent-grade chemicals were purchased from Aldrich Chemical Company and were used as received.

General Method for the Synthesis of 1-Aryl-3-methyl-2-pyrazolin-5-ones **3a-d**.

A mixture of the phenylhydrazine derivative (136 mmoles), ethyl acetoacetate (17.6 g, 136 mmoles) and glacial acetic acid (60 ml) was stirred at reflux for 3-4 hours. The mixture was then evaporated to dryness, and the resultant crude oil crystallized and recrystallized from mixtures of benzene and petroleum ether to yield **3a-d**.

1-Phenyl-3-methyl-2-pyrazolin-5-ones (**3a**).

This compound was obtained as white needles (100%), mp 127-129° (lit [8] mp 127°); ^{1}H nmr (deuteriochloroform): δ 2.16 (s, 3, 3-C*H*$_3$), 3.35 (s, 2, 4-*H*$_2$), 7.1-7.9 (m, 5, Ar*H*); ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 2.13 (s, 3, 3-C*H*$_3$), 5.33 (s, 1, 4-*H*), 7.1-7.8 (m, 5, Ar*H*); ir (deuteriochloroform): 1710 (C=O) cm^{-1}; ir (dimethylsulfoxide-d$_6$): 1655 (C=O) cm^{-1}.

1-(4-Chlorophenyl)-3-methyl-2-pyrazolin-5-one (**3b**).

This compound was obtained as an off-white granular solid (86%), mp 171-173° (lit [8] mp 172°); ^{1}H nmr (deuteriochloroform): δ 2.17 (s, 3, 3-C*H*$_3$), 3.38 (s, 2, 4-*H*$_2$), 7.5 (AB, 4, Ar*H*); ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 2.18 (s, 3, 3-C*H*$_3$), 5.29 (s, 1, 4-*H*), 7.5 (AB, 4, Ar*H*); ir (deuteriochloroform): 1690 (C=O) cm^{-1}; ir (dimethylsulfoxide-d$_6$: 1645 (C=O) cm^{-1}.

1-(4-Methoxyphenyl)-3-methyl-2-pyrazolin-5-one (**3c**).

This compound was obtained as a colorless, granular solid (97%), mp 118-119° (lit [8] mp 122°); ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3, 3-C*H*$_3$), 3.27 (s, 2, 4-*H*$_2$), 7.3 (AB, 4, Ar*H*); ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 2.10 (s, 3, 3-C*H*$_3$), 5.25 (s, 1, 4-*H*), 7.2 (AB, 4, Ar*H*); ir (deuteriochloroform): 1715 (C=O) cm^{-1}; ir (dimethylsulfoxide-d$_6$: 1655 C=O) cm^{-1}.

1-(4-Nitrophenyl)-3-methyl-2-pyrazolin-5-one (**3d**).

This compound was obtained as yellow needles (72%), mp 205-210° (lit [8] mp 220°); ^{1}H nmr (deuteriochloroform): δ 2.27 (s, 3, 3-C*H*$_3$), 3.51 (s, 2, 4-*H*$_2$), 8.2 (AB, 4, Ar*H*); ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 2.13 (s, 3, 3-C*H*$_3$), 5.34 (s, 1, 4-*H*), 8.1 (AB, 4, Ar*H*); ir (deuteriochloroform): 1710 (C=O) cm^{-1}; ir (dimethylsulfoxide-d$_6$): 1650 (C=O) cm^{-1}.

General Method for the Synthesis of 4-Isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones **4a-d**.

A solution of **3a-d** (100 mmole) in acetone (100 ml) was stirred at reflux for 16-24 hours, then cooled (ice bath). Water (100 ml) was added, and the resultant precipitate isolated by filtration and recrystallized from aqueous acetone to give **4a-d**.

4-Isopropylidene-1-phenyl-3-methyl-2-pyrazolin-5-one (**4a**).

This compound was obtained as long, yellow needles (94%), mp 115-116° (lit [2] mp 116°); ^{1}H nmr (deuteriochloroform): δ 2.24 (s, 3, 3-C*H*$_3$), 2.36 (s, 3, C*H*$_3$), 2.53 (s, 3, C*H*$_3$), 7.1-7.9 (m, 5, Ar*H*); ir (chloroform): 1705 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.95; H, 6.63; N, 13.06.

4-Isopropylidene-1-(4-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**4b**).

This compound was obtained as yellow prisms (86%), mp 150-151°; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3, 3-C*H*$_3$), 2.34 (s, 3, C*H*$_3$), 2.54 (s, 3, C*H*$_3$), 7.5 (AB, 4, Ar*H*); ir (chloroform): 1695 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.27; Cl, 14.25. Found: C, 62.73; H, 5.27; N, 11.25; Cl, 14.27.

4-Isopropylidene-1-(4-methoxyphenyl)-3-methyl-2-pyrazolin-5-one (**4c**).

This compound was obtained as long, yellow needles (98%), mp 166-170°; ^{1}H nmr (deuteriochloroform): δ 2.29 (s, 3, 3-C*H*$_3$), 2.35 (s, 3, C*H*$_3$), 2.56 (s, 3, C*H*$_3$), 3.74 (s, 3, OC*H*$_3$), 7.3 (AB, 4, Ar*H*); ir (chloroform): 1700 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.74. Found: C, 68.73; H, 6.63; N, 11.43.

4-Isopropylidene-1-(4-nitrophenyl)-3-methyl-2-pyrazolin-5-one (**4d**).

This compound was obtained as a brown, granular solid (72%), mp 206-209°; ^{1}H nmr (deuteriochloroform + dimethylsulfoxide-d$_6$): δ 2.37 (s, 3, 3-C*H*$_3$); 2.40 (s, 3, C*H*$_3$), 2.57 (s, 3, C*H*$_3$), 8.2 (AB, 4, Ar*H*); ir (chloroform) 1710 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.31; H, 5.09; N, 16.14.

Reaction of **4a-d** with 2,4-Dinitrophenylhydrazine.

A solution of **4a-d** (5.0 mmoles) in ethanol (3.0 ml) was added to a cold (ice bath) solution of 2,4-dinitrophenylhydrazine (0.14 g) in concentrated sulfuric acid (0.1 ml), water (1.0 ml) and ethanol (3.5 ml). This mixture

was stirred at room temperature for 30 minutes, yielding a yellow precipitate. The precipitate was isolated by filtration, washed with water and recrystallized from aqueous ethanol to give **13** (66-92%) as yellow needles, mp 123-124° (lit mp 126°).

Reaction of **4a-d** with Semicarbazide.

A mixture of **4a-d** (2.0 mmoles) semicarbazide (500 mg) and sodium acetate (750 mg) in ethanol (5.0 ml) and water (5.0 ml) was stirred at room temperature for 1 hour, then cooled (ice bath). The resultant white precipitate was isolated by filtration, washed with water (2 x 5 ml) and dried *in vacuo* to give **3a-d** (40-78%) as off-white to yellow solids. Further cooling of the filtrate gave a yellow precipitate which was isolated by filtration and recrystallized from ethanol to give **14**, mp 182-185° (lit mp 187°).

Attempted Conjugate Addition with **4a** Thiophenol, 2-Mercaptoethanol and 3-Mercaptopropionic Acid. Method A.

A mixture of **4a** (5.0 mmoles) and thiol **16**, **17** or **18** (5.0 mmoles) in benzene (30 ml) was stirred at room temperature. Reverse-phase hplc analysis (80% methanol in water of the reaction mixtures over a 72 hour period revealed that no additional product had formed. These observations were confirmed by addition of hexane (30 ml) to the reaction mixture to yield a yellow solid which was isolated and determined to be the starting isopropylidene (^{1}H-nmr).

Method B.

A mixture of **4a** (1.0 mmole) and thiols **17** or **18** (2.0 mmoles) in water (10 ml) and tetrahydrofuran (10 ml) were stirred at room temperature. Monitoring of this reaction by reverse-phase hplc (80% methanol in water) revealed that even after 5 days no addition product had formed.

Attempted Conjugate Addition with Piperidine.

A mixture of **4a** (1.07 g, 5.0 mmoles) and piperidine (0.49 ml, 5.0 mmoles) in benzene (30 ml) was stirred at room temperature. Reverse-phase hplc (80% methanol in water) analysis of the reaction mixture after 48 hours revealed that it contained primarily unreacted **4a** as well as a small quantity of **3a** and several small unidentified peaks. Evaporation of the reaction mixture gave a red oil which, after chromatographic workup (silica gel with dichloromethane as the eluting solvent), gave **4a** (0.84 g, 79%) and **3a** (70 mg, 8.0%).

Synthesis of Nitrile **21**.

A solution of potassium cyanide (1.46 g, 22 mmoles) and ammonium chloride (1.06 g, 19.6 mmoles) in water (8.0 ml) was added to a solution of **4a** (2.4 g, 11.2 mmoles) in ethanol (7.0 ml). This mixture was stirred at reflux for 2 hours, resulting in the formation of a red solution. Evaporation of the reaction mixture gave a pink solid which was suspended in water (50 ml). The aqueous suspension was extracted with ethyl acetate (3 x 50 ml), and the combined ethyl acetate extracts dried (sodium sulfate). Filtration, followed by evaporation of the filtrate solvent gave a pink solid which was crystallized and recrystallized from aqueous ethanol to yield **21** (1.9 g, 70%) as long white needles, mp 145-146°; ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.70 (s, 6, C*H*$_3$); 2.32 (s, 3, C*H*$_3$), 7.1-7.7 (m, 5, Ar*H*); ir (deuteriochloroform): 1710 and 1650 (C=O); ir (dimethylsulfoxide-d_6): 1650 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.27; N, 17.42. Found: C, 69.70; H, 6.31; N, 17.38.

Synthesis of Spiroepoxide **22** and Hydroxy spiroepoxide **23**. Method A.

Hydrogen peroxide (1.5 ml, 30%) was added to a solution of **4a** (1.50 g, 7.0 mmoles) in glacial acetic acid (10 ml) and this mixture stirred at 70° for 2 hours. The reaction mixture was then cooled (ice bath) and neutralized with concentrated ammonium hydroxide to yield a brown oil. This oil crystallized upon addition of ethanol, and the crystals were isolated by filtration and recrystallized from ethanol to give **22** (870 mg, 54%) as yellow needles, mp 71-72°; ^{1}H-nmr deuteriochloroform: δ 1.65 (s, 3, C*H*$_3$), 1.74 (s, 3, C*H*$_3$), 2.17 (s, 3, C*H*$_3$), 7.1-7.9 (m, 5, Ar*H*).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.80; H, 6.13; N, 12.17. Found: C, 67.77; H, 6.21; N, 12.14.

Method B.

A mixture of **4a** (2.34 g, 10.9 mmoles) and *m*-chloroperbenzoic acid (2.52 g, 14.6 mmoles) in benzene (100 ml) was stirred at room temperature for 6 hours. The reaction mixture was then washed successively with saturated potassium carbonate (100 ml), saturated potassium carbonate (2 x 100 ml) and water (100 ml) and then dried (sodium sulfate). Filtration, followed by evaporation of the filtrate solvent yielded a yellow oil. Column chromatography (silica gel with dichloromethane as the eluting solvent yielded the spiroepoxide **22** (1.92 g, 76%) and the hydroxy spiroepoxide **23** (125 mg, 4.6%), mp 129-130°; ^{1}H-nmr (deuteriochloroform); δ 1.70 (s, 3, C*H*$_3$), 2.16 (s, 3, C*H*$_3$), 3.1 (t, 2, O*H*), 4.18 (d, 2, C*H*$_2$); 7.1-7.8 (m, 5, Ar*H*).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.52; H, 5.75; N, 11.32.

Hydrolysis of **4a-d**. Method A.

A suspension of **4a-d** (10 mmoles) in 6*N* hydrochloric acid (50 ml) was stirred at room temperature until hplc evaluation (60% methanol in water) revealed that hydrolysis was complete (4-8 hours). The reaction mixture was then neutralized with 1*N* sodium hydroxide, and the resultant precipitate extracted into ether (3 x 50 ml). The combined ether extracts were washed with water (100 ml) and dried sodium sulfate. Filtration, followed by evaporation, of filtrate solvent gave **3a-d** (72-88%) as off-white solids.

Method B.

A solution of **4a-d** (10 mmoles) in 48% hydrobromic acid (10 ml) was stirred at reflux for 4 hours, then cooled to room temperature. Evaporation of the acid gave a colored solid which was suspended in water (20 ml) and neutralized with saturated sodium bicarbonate (100 ml). This aqueous suspension was extracted with ether (3 x 75 ml) and the ether extracts combined, washed with water (100 ml) and dried sodium sulfate. Filtration, followed by evaporation of the filtrate solvent gave **3a-d** and **3d-e** (66-92%).

Catalytic Reduction of **4a-d**.

A suspension of **4a-d** (2.0 mmole) in ethanol (100 ml) containing concentrated hydrochloric acid (1.0 ml) and 5% Palladiuman carbon (250 mg) was shaken under a hydrogen atmosphere (initial psi of 50) on a Parr apparatus until the uptake of hydrogen ceased (3-6 hours). Filtration of the reaction mixture, followed by evaporation of the filtrate solvent yielded a yellow oil. This oil was suspended in water (25 ml) and the aqueous suspension neutralized with sodium bicarbonate. The resulting solid was isolated by filtration and recrystallized from aqueous methanol to give **28a-d** (50-80%).

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