# Synthesis and Reactions of Derivatives of 6-Imino-2,4-cyclohexadien-1-ols

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*Received October 5, 1979*

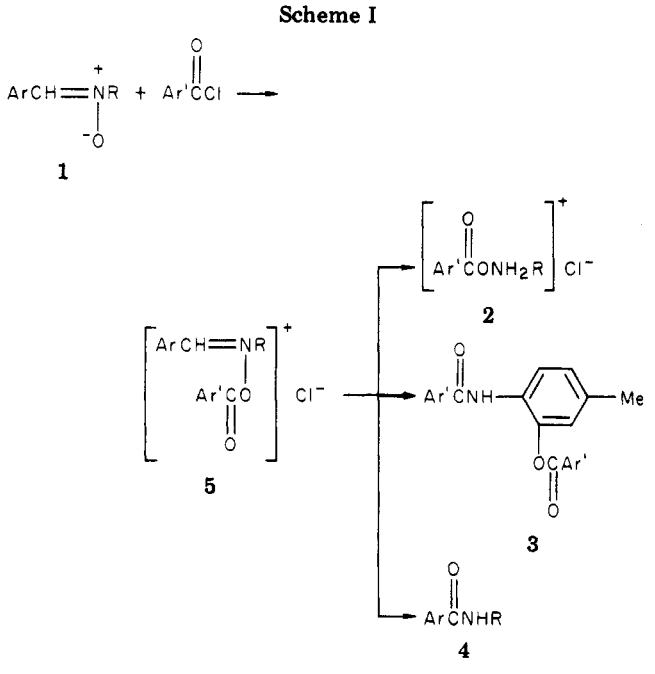
α-(*p*-Nitrophenyl)-*N*-(2,6-dimethylphenyl)nitrone (**6a**) and α-(*p*-nitrophenyl)-*N*-(2,4,6-trimethylphenyl)nitrone (**6b**) are isomerized by *p*-nitrobenzoyl chloride in anhydrous ether into *N*-(2,6-dimethylphenyl)-*p*-nitrobenzamide (**7a**) and *N*-(2,4,6-trimethylphenyl)-*p*-nitrobenzamide (**7b**), respectively. The same reagents in commercial acetone form the *p*-nitrobenzoate esters of 6-imino-1,5-dimethyl- and 6-imino-1,3,5-trimethyl-2,4-cyclohexadien-1-ol hydrochlorides (**8a,b**). The free bases of **8a,b** (**13** and **19**) react with triphenylphosphine to form triphenylphosphine oxide and **7a** and **7b**, respectively. In refluxing toluene **13** isomerizes to 2,6-dimethyl-4-(*p*-nitrobenzoyloxy)aniline. Compound **20**, the *N*-*p*-nitrobenzoyl derivative of **19**, isomerizes in refluxing toluene to *N*-(*p*-nitrobenzoyl)-2,6-dimethyl-4-[(*p*-nitrobenzoyloxy)methyl]aniline. When treated with KCN in DMF, **20** forms *N*-(*p*-nitrobenozyl)-3-cyano-2,4,6-trimethylaniline while in $CHCl_3$ containing HCl **20** is transformed into *N*-(*p*-nitrobenzoyl)-3-chloro-2,4,6-trimethylaniline. Reaction of **6a,b** with $SOCl_2$ in $C_6H_6$ gave 2,6-dimethyl- and 2,4,6-trimethyl-3-chloroaniline hydrochloride, respectively.

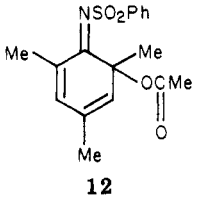
We recently reported that in moist solvents aroyl chlorides react with α-aryl-*N*-alkylnitrones (**1**) to give *N*-alkyl-*O*-aroylhydroxylamine hydrochlorides (**2**) and aldehydes (Scheme I).[1] Under similar conditions α-phenyl-*N*-*p*-tolylnitrone (**1**, R = *p*-$MeC_6H_4$) with 2 equiv of aroyl chloride formed *N*-aroyl-2-(aroyloxy)-4-methylanilines (**3**). In anhydrous solvents the aroyl chlorides isomerized both α-aryl-*N*-alkyl- and α,*N*-diarylnitrones to the corresponding amides **4**. All of these reactions can be rationalized by presuming the formation of an (aroyloxy)(benzylidene)ammonium chloride (**5**, Scheme I).[1,2] Our continued interest in these reactions prompted us to examine the reaction of aroyl chlorides with nitrones containing an *N*-(2,6-dialkylaryl) and an *N*-(2,4,6-trialkylaryl) moiety. The products were derivatives of 6-imino-2,4-cyclohexadien-1-ols whose chemistry is delineated here. This paper also includes a study of the reaction of the above nitrones with thionyl chloride.

Reaction of α-(*p*-nitrophenyl)-*N*-(2,6-dimethylphenyl)- and α-(*p*-nitrophenyl)-*N*-(2,4,6-trimethylphenyl)nitrones (**6a,b**) with *p*-nitrobenzoyl chloride in anhydrous ether leads to the isomeric amides **7a,b** while in commercial acetone the products of reaction are the *p*-nitrobenzoates of 6-imino-2,4-cyclohexadien-1-ol hydrochlorides **8a,b** formed in 45 and 55% yields, respectively, and *p*-nitrobenzaldehyde (Scheme II). Similarly, **6a** admixed with *p*-chlorobenzoyl chloride in acetone gave **8c** (Ar = *p*-$ClC_6H_4$). The structures of **8a,b** were elucidated by spectroscopic analysis, elemental analysis, and the hydrolysis of **8a** to the known 6-(*p*-nitrobenzoyloxy)-2,6-dimethyl-2,4-cyclohexadienone (**9a**)[3] (Scheme II). The reaction of **6a,b** with *p*-nitrobenzoyl chloride in acetone probably occurs by the initial formation of the (aroyloxy)(benzylidene)ammonium chloride **10** which rearranges to **11**. Hydrolysis of **11** forms **8a,b**.

Substances related to **8**, namely, **9** and **12**, had been prepared previously by treating phenols with diaroyl peroxides[3] and *N*-benzenesulfonyl-2,4,6-trimethylaniline with lead tetraacetate,[4a-c] respectively. Compounds **8a,b** and their derivatives undergo reactions both similar and dissimilar to those observed for **9** and **12**.

Scheme I

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The free base of **8a**, namely, **13**, in refluxing toluene rearranges to **14** (Scheme III). The structure of **14** was established by its conversion to **15** and by spectroscopic analysis (e.g., the infrared spectrum exhibited the asymmetric and symmetric stretches of the amino group at 3496 and 3412 $cm^{-1}$ and ester group absorption bands at 1727 and 1261 $cm^{-1}$). Compound **15** was also prepared by treating 2,6-dimethyl-4-hydroxyaniline with 2 equiv of *p*-nitrobenzoyl chloride. Reaction of **13** with *p*-nitrobenzoyl chloride afforded **16** in 85% yield, and thermolysis of **16** in refluxing decalin formed **15** in quantitative yield (Scheme III). The isomerization of **13** to **14** is analogous to the isomerization of **9a** and **17** (Ar = Ph) in refluxing toluene into **18a** and **18b**, respectively.[3]

(1) R. H. Heistand, M. A. Stahl, and H. W. Heine, *J. Org. Chem.*, 43, 3613 (1978).
(2) M. Lamchen in "Mechanisms of Molecular Migrations", Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, 1968, pp 1-60.
(3) D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *J. Chem. Soc. C*, 2231 (1971).
(4) (a) R. Adams and K. R. Brower, *J. Am. Chem. Soc.*, 78, 4770 (1956); (b) R. Adams, E. J. Agnello, and R. S. Colgrove, *ibid.*, 77, 5617 (1955); (c) R. Adams and J. E. Dunbar, *ibid.*, 78, 4774 (1956).

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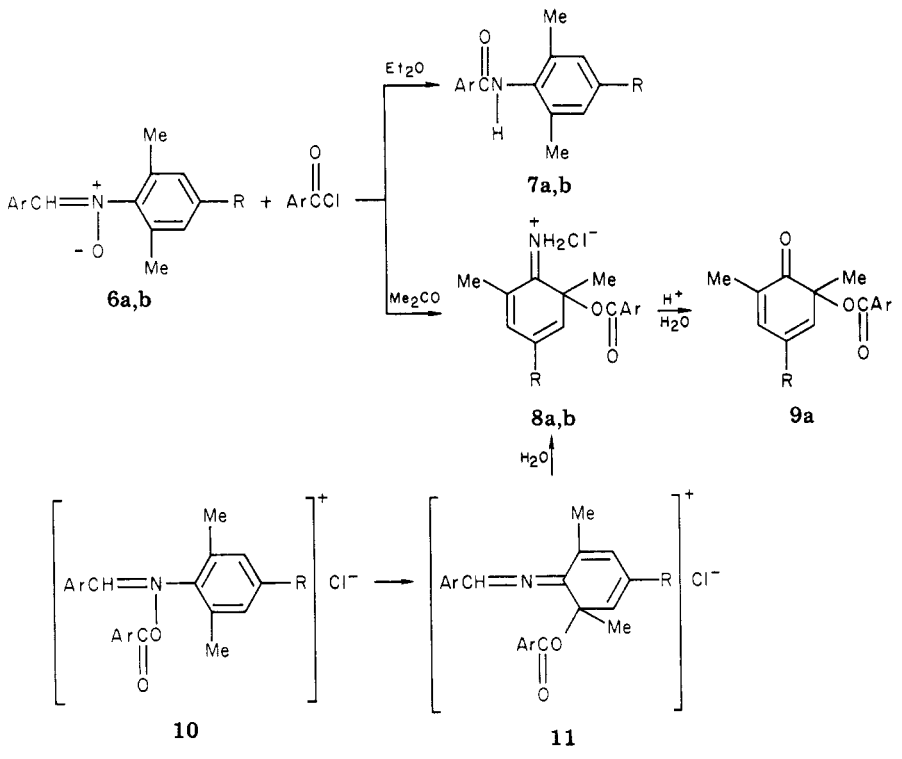
Scheme II[a]



[a] For 6a, 7a, 8a, and 9a R = H, for 6b, 7b, and 8b R = Me, and Ar = $p$-$O_2NC_6H_4$.

In contrast to the thermolysis of **16** which afforded **15**, compound **20** (prepared by the $p$-nitrobenzoylation of **19**) isomerized in refluxing toluene to **21** (Scheme III). Structural proof of **21** rested upon $^1$H NMR spectroscopy, IR spectroscopy, mass spectroscopy, and elemental analysis. It is interesting to note that **9b** in refluxing toluene gave a mixture of **9b** and **22**.[3] No product comparable to **21** (e.g., 2,6-dimethyl-4-[($p$-nitrobenzoyloxy)methyl]phenol, **23**) was observed (Scheme III).

Two interpretations seem reasonable for the isomerization of **20** into **21**. Either **20** rearranges to **24** which eliminates $p$-nitrobenzoic acid to give **25**, followed by the addition of $p$-nitrobenzoic to **25** to form **21**, or **20** ionizes to the ion pair **26**. Loss of a proton from the cation of **26** then produces **25** (Scheme IV).

Cyanide ion in DMF or triphenylphosphine in ether converts **13** and **19** into **7a** and **7b**, respectively. These transformations possibly proceed by the addition of the nucleophile to the imino carbon of **13** and **19** to give the anion **27**. The proximity of the negatively charged nitrogen of **27** to the carbonyl carbon facilitates the formation of **28** which subsequently isomerizes to **29**. Expulsion of cyanate ion or triphenylphosphine oxide from **29** produces **7a** or **7b** (Scheme V). In the triphenylphosphine experiments it was possible to isolate triphenylphosphine oxide. Further support for this scheme derives from the observation that **30** adds hydrogen cyanide to give **31**[4c] (Scheme V).

In contrast to the interaction of **13** and **19** with cyanide ion, compound **20** in DMF solutions containing cyanide ion formed **32**. Similarly, **16** and **20** with hydrogen chloride in chloroform produced **33a,b** (Scheme VI). These conversions are analogous to both the reaction of **12** with the same reagents to form **34** and **35**,[4a] respectively, and the reaction of **36** with cyanide ion to give 5-cyano-2,4-dimethylphenol (**37**,[3] Scheme VI). Adams and colleagues[4a] have shown convincingly that reaction of nucleophiles with **12** (and by analogy **20**) proceeds via the intermediacy of **38** (Scheme VI).

In an attempt to prepare the chloro analogues of **8a,b**, nitrones **6a,b** were reacted with thionyl chloride in benzene. The products isolated were 2,6-dimethyl-3-chloro- and 2,4,6-trimethyl-3-chloroaniline hydrochlorides **39** and **40**, respectively, and $p$-nitrobenzaldehyde (Scheme VII). Compound **40** was characterized by its reaction with benzenesulfonyl chloride to give the known benzenesulfonanilide derivative, by its conversion to **33b**, and by mass spectroscopy. Compound **39**'s structure was confirmed by conversion to the known acetanilide and to **33a**. A rationale for the reaction of thionyl chloride with **6a,b** involves formation of **41**, which loses sulfur dioxide to yield **42**. Migration of the chlorine gives **43**. Subsequent aromatization of **43** and hydrolysis forms **39**, **40**, and $p$-nitrobenzaldehyde (Scheme VII). Another possibility is that **42** interacts with chloride ion to give **39** and **40** much like the reaction of **16** and **20** with hydrogen chloride to yield **33a,b**. Support for the likelihood of **42** as an intermediate stems from the known reaction of $\alpha$,$N$-diarylnitrones with thionyl chloride in benzene to give $N$-(benzylidene)-2-chloroaniline hydrochlorides (**44**,[5] Scheme VII).

## Experimental Section

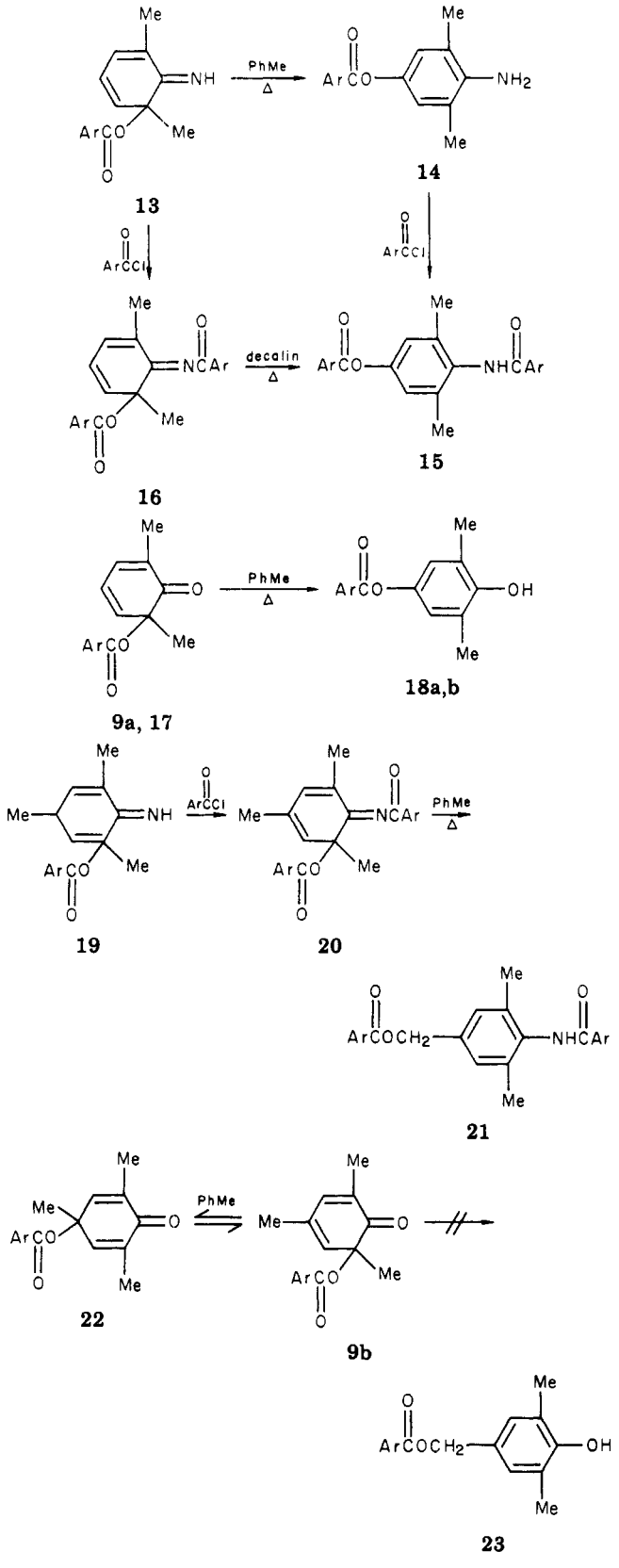
**$\alpha$-($p$-Nitrophenyl)-$N$-(2,6-dimethylphenyl)nitrone (6a).** To 2.74 g (20 mmol) of $N$-(2,6-dimethylphenyl)hydroxylamine[6] in 20 mL of EtOH was added a solution of 3.02 g (20 mmol) of $p$-nitrobenzaldehyde in 20 mL of EtOH. The reaction mixture was warmed at 40–50 °C for 0.5 h and allowed to stand an additional 2 h. The precipitate or **6a** (4.49 g, 83%; mp 198–200 °C) was filtered and recrystallized from ethanol to give **6a**: 3.92 g (73%); mp 200–201.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.44 (AA′BB′, 4 H), 7.86 (s, 1 H), 7.18 (s, 3 H), 2.35 (s, 6 H); IR (Nujol) 1589, 1499, 1326, 1191, 1096, 777 cm$^{-1}$. Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.43; H, 5.51; N, 10.26.

**$p$-Nitrobenzoate Ester of 6-Imino-1,5-dimethyl-2,4-cyclohexadien-1-ol Hydrochloride (8a) and 13.** To a stirred solution

(5) D. Liotta, A. D. Baker, S. Goldstein, N. L. Goldman, F. Weinstein-Lanse, D. Felsen-Reingold, and R. Engel, *J. Org. Chem.*, **39**, 2718 (1974).

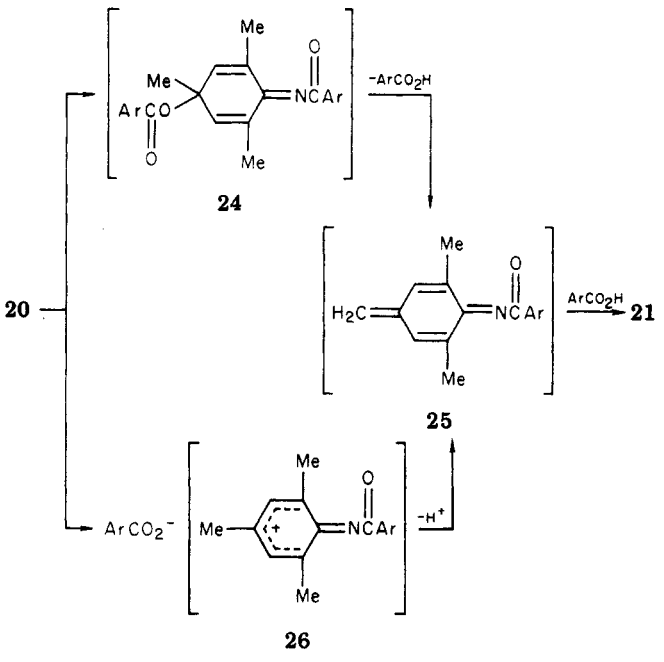
(6) E. Bamberger, *Chem. Ber.*, **57**, 2083 (1924).

Scheme III[a]

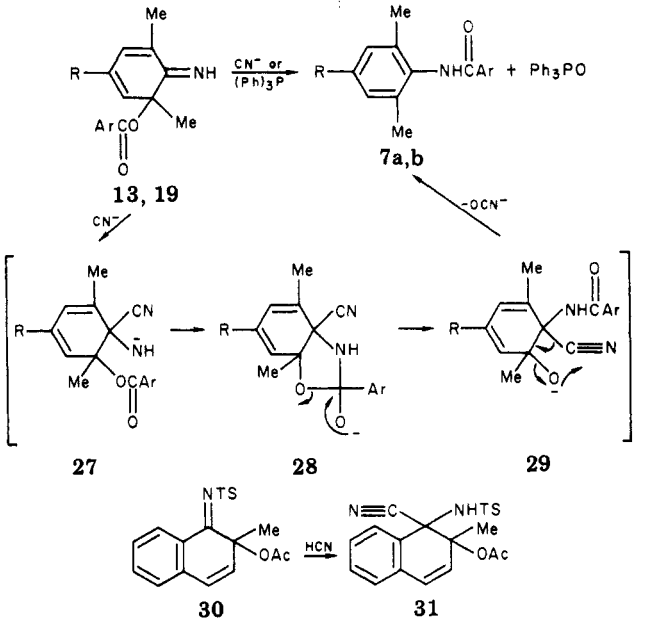


[a] For 9a,b, 13–16, 18a, and 19–23 Ar = $p$-$O_2NC_6H_4$; for 17 and 18b Ar = $C_6H_5$.

Scheme IV



Scheme V[a]



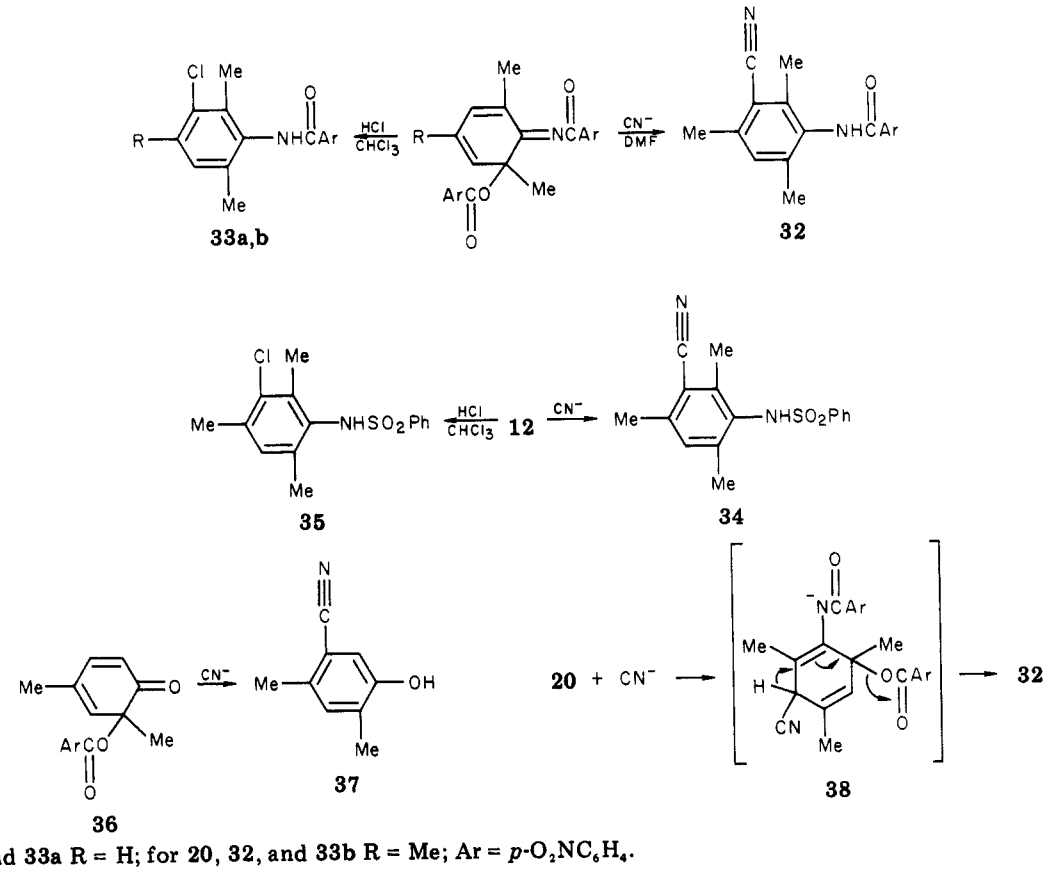
[a] For 7a and 13 R = H; for 7b and 19 R = Me.

of **6a** (541 mg, 2.0 mmol) in 12 mL of acetone was added $p$-nitrobenzoyl chloride (371 mg, 2.0 mmol). After 10 h the precipitate of **8a** [283 mg (44%), mp 154–157.5 °C dec] was filtered and washed with 5 mL of dry ether. Recrystallization from MeOH/$Et_2O$ (1:10) gave **8a**: mp 160–163 °C; mass spectrum, $m/e$ 286 ($M^+$ – HCl); $^1H$ NMR ($CDCl_3$) $\delta$ 8.34 (AA′BB′, 4 H), 7.10 (m, 1 H), 6.43 (m, 2 H), 2.40 (s, 3 H), 1.90 (s, 3 H); IR (Nujol) 2710, 1718, 1640, 1630, 1272, 1055, 863, 808, 714 $cm^{-1}$. Compound **13** was obtained by stirring a mixture of **8a** (100 mg, 0.311 mmol), $Et_3N$ (120 mg, 1.2 mmol), and 20 mL of dry benzene. The precipitate of $Et_3N$·HCl (125 mg, 91%) was filtered and the filtrate evaporated to give **13**: 84 mg (84%); mp 109–110 °C dec. Recrystallization from 1:1 $Et_2O$/petroleum ether (bp 65–73 °C) formed platelets of **13**, mp 111.5–113.0 °C dec. Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.19; H, 4.98; N, 9.61.

***p*-Nitrobenzoate Ester of 6-Imino-1,3,5-trimethyl-2,4-cyclohexadien-1-ol Hydrochloride (8b) and 19.** $p$-Nitrobenzoyl chloride (371 mg, 2.0 mmol) was added with stirring to a solution of **6b**[7] (586 mg, 2.0 mmol) in 12 mL of $Me_2CO$. The mixture was stirred for 1 h, and the precipitate of **8b** [324 mg (48%), mp 136–139.5 °C dec] was filtered and washed with 5 mL of dry $Et_2O$. Recrystallization from cyclohexane/MeOH (10:1) gave **8b** (220 mg, 33%) which in a prewarmed (140 °C) melting point apparatus

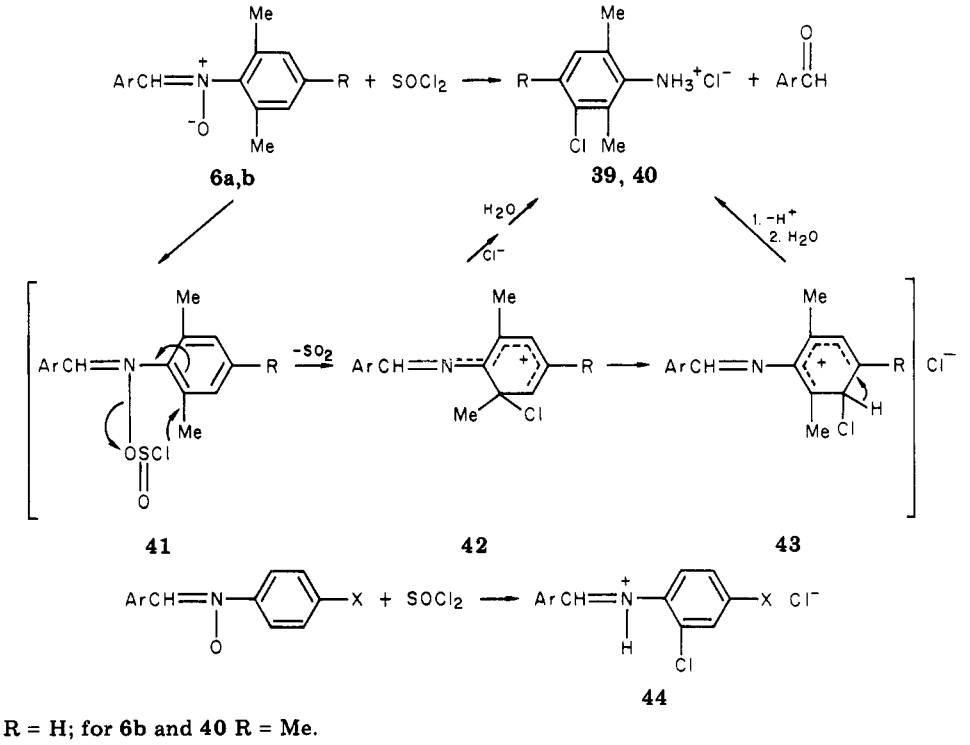
(7) E. Bamberger and A. Rising, *Chem. Ber.*, **33**, 3623 (1900).

**Scheme VI**[a]



[a] For **16** and **33a** R = H; for **20**, **32**, and **33b** R = Me; Ar = $p$-$O_2NC_6H_4$.

**Scheme VII**[a]



[a] For **6a** and **39** R = H; for **6b** and **40** R = Me.

decomposed at 148–151 °C: mass spectrum, $m/e$ 300 ($M^+$ – HCl); $^1H$ NMR ($CDCl_3$) $\delta$ 12.3–11.6 (m, 2 H), 8.33 (AA'BB', 4 H), 6.90 (s, 1 H), 5.98 (s, 1 H), 2.38 (s, 3 H), 2.03 (s, 3 H), 1.86 (3 H); IR (Nujol) 1730, 1264 $cm^{-1}$. Compound **19** was obtained by stirring **8b** (200 mg, 0.6 mmol) in 40 mL of dry benzene containing $Et_3N$ (100 mg, 1.0 mmol). The $Et_3N$·HCl was filtered and the filtrate evaporated. The crude **19** [171 mg (95%), mp 66–69 °C dec] was recrystallized from petroleum ether (bp 30–60 °C) to give **19**: 112 mg (62%); mp 84–87 °C dec; IR (Nujol) 3300, 1718, 1510, 1333, 1272 $cm^{-1}$. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.90; H, 5.32; N, 9.14.

**$p$-Chlorobenzoate Ester of 6-Imino-1,5-dimethyl-2,4-cyclohexadien-1-ol Hydrochloride (8c).** A solution of $p$-chlorobenzoyl chloride (350 mg, 2 mmol) was added all at once to a mixture of **6a** (541 mg, 2.0 mmol) in 12 mL of acetone. The reaction mixture was stirred overnight, and the **8c** [136 mg (22%),

mp 154–158 °C dec] that had formed was filtered. Recrystallization from MeOH/$Et_2O$ (1:1) gave **8c**: 87 mg (14%); mp 159.5–163.5 °C dec; $^1H$ NMR ($Me_2SO$) $\delta$ ~8 (br signal, 2 H), 7.85 (AA'BB', 4 H), 7.38 (m, 1 H), 6.56 (d, 2 H), 2.29 (s, 3 H), 1.78 (s, 3 H); IR (Nujol) 2940–2600 (br band), 1718, 1656, 1637, 1284, 1272 $cm^{-1}$. Anal. Calcd for $C_{15}H_{15}NO_2Cl_2$: C, 57.71; H, 4.84; N, 4.49. Found: C, 58.18; H, 5.02; N, 4.31.

**Isomerization of 6a to 7a.** A mixture of **6a** (541 mg, 2 mmol), 12 mL of dry $Et_2O$, and *p*-nitrobenzoyl chloride (370 mg, 2 mmol) was stirred 24 h. The crude **7a** was filtered and the filtrate evaporated. The residue containing some **7a**, *p*-nitrobenzoic acid, and *p*-nitrobenzoyl chloride was extracted into $CH_2Cl_2$, and the extract of $CHCl_2$ was washed with 10% $Na_2CO_3$ and dried ($MgSO_4$). All of the **7a** was pooled and recrystallized from 95% EtOH: yield 94%; mp 190–191.5 °C (lit.[8] mp 193–196 °C).

**Isomerization of 6b to 7b.** By use of the procedure described for the isomerization of **6a**, compound **6b** gave **7b**: yield 89%, mp 226.5–228 °C (lit.[8] mp 223–224 °C).

**Conversion of 8a (13) to 9a.** A solution of **13** (322 mg, 1 mmol) in 10 mL of 95% EtOH and 1 drop of 5% hydrochloric acid was refluxed for 15 min. The solvent was evaporated, and $H_2O$ (15 mL) and $Et_2O$ (15 mL) were added to the residue. After the mixture was vigorously shaken, the ether layer was separated, dried ($MgSO_4$), and evaporated to give **9a**: 202 mg (63%); mp 148–152 °C. Recrystallization from MeOH gave **9a**: 113 mg (35%); mp 153–155 °C (lit.[4] mp 154–155 °C). The infrared spectra of **9a** prepared by this procedure and an authentic sample supplied by Professor D. Barton were identical.

**Conversion of 13 to 7a.** A mixture of **13** (200 mg, 0.698 mmol), KCN (50 mg), and 6 mL of DMF was stirred for 24 h. Water (50 mL) was added to the mixture, and the crude **7a** (138 mg, 73%) was filtered. Recrystallization from EtOH/$H_2O$ (2:1) gave **7a**: 102 mg (54%); mp 196–196.5 °C. The infrared spectrum of **7a** was identical with that of **7a** prepared by the isomerization of **6a**. The same conversion occurred when a suspension of **13** (200 mg), $Et_2O$ (6 mL), and $(Ph)_3P$ (184 mg) was stirred for 24 h. Evaporation of the solvent and recrystallization of the residue with EtOH/$H_2O$ (2:1) afforded **7a**: 101 mg (53%); mp 195–196 °C.

**Isomerization of 13 to 14.** A solution of **13** (1.50 g, 5.23 mmol) in 150 mL of PhMe was refluxed 24 h. Evaporation of the solvent gave 985 mg of material melting from 175–190 °C with decomposition. Recrystallization from *t*-BuOH formed **14**: 739 mg (49%); mp 174–175.5 °C (after the sample melted, solidification occurred followed by remelting at 188.5–189 °C with decomposition); $^1H$ NMR ($CDCl_3$) $\delta$ 8.46 (s, 4 H), 6.98 (s, 2 H), 3.8 (br signal, 2 H), 2.38 (s, 6 H); IR (Nujol) 3546, 3436, 1746, 1642, 1533, 1349, 1267, 1236 $cm^{-1}$; mass spectrum, *m/e* 286 (molecular ion). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.33; H, 4.98; N, 9.56. Reaction of **14** with *p*-$O_2NC_6H_4COCl$ gave **15**: yield 60%; mp 317–318 °C.

***N*-(*p*-Nitrobenzoyl)-2,6-dimethyl-4-(*p*-nitrobenzoyloxy)-aniline (15).** *p*-Nitrobenzoyl chloride (372 mg, 2.0 mmol) was added to a stirred solution of 2,6-dimethyl-4-hydroxyaniline (137 mg, 1 mmol) and $Et_3N$ (220 mg, 2.2 mmol) in 20 mL of dry benzene. The mixture was refluxed 3 h and cooled, and $H_2O$ (5 mL) was added. Filtration gave **15**: 432 mg (99%); mp 312–317 °C. Recrystallization from $Me_2SO$/MeOH (5:1) formed crystals of **15**: 292 mg (67%); mp 319–321 °C; mass spectrum, *m/e* 435 (molecular ion). Anal. Calcd for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94; N, 9.65. Found: C, 60.49; H, 4.10; N, 9.81.

***p*-Nitrobenzoate Ester of 6-(*p*-Nitrobenzoylimino)-1,5-dimethyl-2,4-cyclohexadien-1-ol (16).** *p*-Nitrobenzoyl chloride (155 mg, 0.836 mmol) was added to a stirred solution of **13** (239 mg, 0.836 mmol) and $Et_3N$ (110 mg, 1.1 mmol) in 5 mL of anhydrous benzene. After 5.5 h the $Et_3N$·HCl (101 mg, 89%) was filtered and the filtrate evaporated to give **16**: 311 mg (85%); mp 157–161 °C. Recrystallization from MeOH gave **16** (214 mg, 57%) which melted at 165.5–168 °C and then solidified and remelted at 280–286 °C. The higher melting solid was identified as **15**. For **16**: $^1H$ NMR $\delta$ 7.98 (AA'BB', 4 H), 7.90 (s, 4 H), 6.84 (m, 1 H), 6.2 (m, 2 H), 2.21 (s, 3 H), 1.94 (s, 3 H); IR (Nujol) 1730, 1667, 1639, 1524, 1342, 1276, 1242 $cm^{-1}$; mass spectrum, *m/e* 335 (molecular ion). Anal. Calcd for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94; N, 9.65. Found: C, 60.21; H, 3.85; N, 9.15.

**Isomerization of 16 to 15.** A solution of 200 mg of **16** in 8 mL of decalin was refluxed for 2 h. The solution was cooled, and the 196 mg (98%) of **15**, mp 312–316 °C dec, was filtered. The infrared spectrum was identical with that of **15** prepared by the di-*p*-nitrobenzoylation of 2,6-(dimethylphenyl)-4-hydroxyaniline.

**Conversion of 19 to 7b.** A mixture of **19** (424 mg, 1.41 mmol) and KCN (100 mg, 1.54 mmol) in 12 mL of DMF was stirred for 41 h. Dry ether (50 mL) was added and the reaction mixture filtered. The filtrate was evaporated and $H_2O$ (20 mL) added to the residue. The solid **7b** [172 mg (60%), mp 222–225 °C] was filtered. An additional 50 mg of very crude **7b** precipitated from the filtrate. Recrystallization of 172 mg of **7b** afforded pure **7b**: yield 125 mg; mp 230–232 °C.

***p*-Nitrobenzoate Ester of 6-(*p*-Nitrobenzoylimino)-1,3,5-trimethyl-2,4-cyclohexadien-1-ol (20).** *p*-Nitrobenzoyl chloride (93 mg, 0.5 mmol) was added to a stirred solution of **19** (150 mg, 0.5 mmol) and $Et_3N$ (75 mg, 0.75 mmol) in 5 mL of dry benzene. After 1 h the $Et_3N$·HCl (59 mg, 86%) was filtered and the solvent evaporated. The residual gum was triturated with petroleum ether (bp 63–75 °C). The solid **20** [191 mg (85%), mp 127–131 °C dec] was filtered and recrystallized from MeOH to afford **20**: 106 mg (47%); mp 138–141.5 °C dec; $^1H$ NMR $\delta$ 7.98 (AA'BB', 4 H), 7.90 (s, 4 H), 6.72 (s, 1 H), 5.75 (s, 1 H), 2.10 (s, 3 H), 1.98 (s, 3 H), 1.85 (s, 3 H); IR (Nujol) 1721, 1655, 1623, 1522, 1340, 1264, 1251 $cm^{-1}$; mass spectrum, *m/e* 449 (molecular ion). Anal. Calcd for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26; N, 9.35. Found: C, 61.28; H, 4.47; N, 8.90.

**Isomerization of 20 to 21.** A solution of **20** (140 mg, 0.31 mmol) in 25 mL of toluene was refluxed for 12 h. The reaction mixture was cooled, and **21** (112 mg, mp 224–226 °C) precipitated and was filtered. Evaporation of the filtrate afforded additional **21** (25 mg). The total yield of crude **21** was 96%. Recrystallization from 1-PrOH gave **21**: 98 mg (71%); mp 226.5–228 °C; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 10.27 (s, 1 H), 8.45 (2 AA'BB', 8 H), 7.34 (s, 2 H), 5.43 (s, 2 H), 2.30 (s, 6 H); IR (Nujol) 3268, 1727, 1642, 1515, 1340, 1267 $cm^{-1}$; mass spectrum, *m/e* 449 (molecular ion). Anal. Calcd for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26; N, 9.35. Found: C, 61.38; H, 4.22; N, 9.30.

***N*-(*p*-Nitrobenzoyl)-3-chloro-2,6-dimethylaniline (33a).** Hydrogen chloride was passed through a solution of 879 mg (2.02 mmol) of **16** in 100 mL of $CHCl_3$ for 15 min. The reaction mixture was washed twice with 50-mL portions of 10% $NaHCO_3$. The chloroform layer was dried over $MgSO_4$, filtered, and evaporated. The crude **33a** (507 mg, 83%) melted at 210–213 °C. An analytical sample prepared by recrystallization from $Me_2SO/H_2O$ (1:10) melted at 218–210 °C. Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.22. Found: C, 59.16; H, 4.25; N, 9.12.

***N*-(*p*-Nitrobenzoyl)-3-chloro-2,4,6-trimethylaniline (33b).** A stream of hydrogen chloride was passed into a solution of **20** (250 mg, 0.55 mmol) in anhydrous $CHCl_3$ (50 mL) for 30 min. The *p*-nitrobenzoic acid (93 mg, 90%) that precipitated was filtered and the filtrate washed with 5% $NaHCO_3$. The chloroform layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The crude **33b** was slurried with 5 mL of cold toluene and filtered to give **33b**: 147 mg (83%); mp 215–220 °C. Recrystallization from EtOH/$H_2O$ (1:5) formed crystals of **33b**: 197 mg (61%); mp 224.0–225.5 °C; mass spectrum, *m/e* 318 (molecular ion); $^1H$ NMR $\delta$ 8.13 (AA'BB', 4 H), 7.03 (s, 1 H), 2.37 (s, 3 H), 2.26 (s, 3 H), 2.17 (s, 3 H), 1.60 (s, 1 H); IR (Nujol) 3340, 1670, 1620, 1545, 1345, 1270, 1110, 1016, 1005, 870, 855, 818, 718 $cm^{-1}$. Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.31; H, 4.74; N, 8.78. Found: C, 60.63; H, 4.94; N, 8.73.

**Alternate Synthesis of 33b.** A mixture of 3-chloro-2,4,6-trimethylaniline hydrochloride (410 mg, 2.0 mmol), 10 mL of $Et_2O$, and 10 mL of 10% NaOH was vigorously stirred, and the two layers were separated. To the ether layer were added $Et_3N$ (242 mg, 2.4 mmol) and a solution of *p*-nitrobenzoyl chloride (370 mg, 2 mmol) in 10 mL of dry ether. The mixture was stirred 1 h, and the $Et_3N$·HCl (219 mg, 80%) was filtered. The filtrate was evaporated, and the crude **33b** [477 mg (75%), mp 215–220 °C] was recrystallized from ethanol to give crystals, mp 223–225 °C.

***N*-(*p*-Nitrobenzoyl)-3-cyano-2,4,6-trimethylaniline (32).** A mixture of **20** (200 mg, 0.45 mmol), KCN (40 mg, 0.61 mmol), and 15 mL of DMF was stirred for 3 h. A precipitate of potassium

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*p*-nitrobenzoate (92%) that had formed was filtered. Dropwise addition of $H_2O$ (~10 mL) to the filtrate precipitated **32**: 83.6 mg (61%); mp 224.0–225.0 °C. Recrystallization from *t*-BuOH/$H_2O$ (1:5) formed **32**: 54.8 mg (40%); mp 225–225.5 °C; $^1H$ NMR ($CDCl_3$) δ 8.27 (AA'BB',4 H), 7.17 (s, 1 H), 2.52 (s, 3 H), 2.47 (s, 3 H), 2.28 (s, 3 H), 1.62 (s, 1 H); IR (Nujol) 3300, 2225, 1670, 1540, 1520, 1370, 1350, 1320, 1295, 1110, 1008, 914, 878, 864, 858, 826, 735, 708 $cm^{-1}$. Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.86; N, 13.39. Found: C, 66.08; H, 4.85; N, 13.39.

**2,4,6-Trimethyl-3-chloroaniline Hydrochloride (40).** To a solution of 810 mg (3.0 mmol) of **6b** in 15 mL of dry $C_6H_6$ was added a solution of 390 mg (2.89 mmol) of $SOCl_2$ in 3 mL of dry $C_6H_6$. The reaction mixture was stirred for 10 h and the **40** filtered. The filtrate was evaporated, and 20 mL of $Et_2O$ was added to the residue. The resulting suspension was stirred 0.5 h and the additional **40** filtered. The two portions of **40** were combined and washed with ether to give 377 mg (63%) of crystals, mp 195–209 °C. Treatment of the free base of **40** with benzenesulfonyl chloride gave the known benzenesulfonanilide of **40**; mp 161–164 °C (lit.[9] 163–164 °C).

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**2,6-Dimethyl-3-chloroaniline Hydrochloride (39).** A solution of 1.42 g (5.24 mmol) of $SOCl_2$ in 11 mL of dry $C_6H_6$ was added slowly to a solution of 3.27 g (0.28 mmol) of **6a** in 75 mL of dry $C_6H_6$. The reaction mixture was stirred for 5 h and filtered. The crude **39** was slurried with ether for 10 min and filtered to give 1.71 g (74%) of **39**, mp 202–211 °C dec. Treatment of **39** with acetyl chloride gave the known acetanilide, mp 142–143 °C (lit.[10] 146–147°), and treatment of **39** with *p*-nitrobenzoyl chloride gave **33a**.

**Acknowledgment** is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Camille and Henry Dreyfus Foundation for support of this research. We thank Dr. William VandenHeuvel of Merck Sharp & Dohme Research Laboratories for obtaining the mass spectra of many of the new compounds described here. We also thank Professor D. H. R. Barton for a sample of 2,6-dimethyl-6-(*p*-nitrobenzoyloxy)-cyclohexa-2,4-dienone.

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# Synthesis of 2*H*-Isoindole-4,7-diones by 1,3-Dipolar Addition of Oxazolium 5-Oxides to 1,4-Quinones

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*Received August 15, 1979*

A general, convenient synthesis of 2*H*-isoindole-4,7-diones from readily available starting materials is described. 3-Methyl-2,4-diphenyloxazolium 5-oxide, formed by dehydrative cyclization of *N*-methyl-*N*-benzoyl-*C*-phenylglycine, combines with 1,4-quinones to produce 2*H*-isoindole-4,7-diones in moderate yields. Conversion of other *N*-acyl amino acids to the corresponding less stable oxazolium 5-oxides in solution using 1 equiv of acetic anhydride or dicyclohexylcarbodiimide and subsequent reaction with 1,4-quinones also affords 2*H*-isoindole-4,7-diones.

Two reports on the synthesis of selected 2*H*-isoindole-4,7-diones (**1**) by photolysis of 2,3-diphenyl-2*H*-azirine in the presence of 1,4-quinones[1] and by zinc-induced intramolecular cyclization of 1,2,5-trimethyl-3,4-bis(bromoacetyl)pyrrole followed by dehydrogenation[2] have appeared. We are prompted to report the development of a general, convenient method for preparing this heterocyclic quinone system from readily available starting materials, i.e., *N*-acyl amino acids and 1,4-quinones.

We have previously reported[3] the 1,3-dipolar addition of 3-methyl-2,4-diphenyloxazolium 5-oxide (**2a**) to cyclopentadienequinone and to anthracenequinone. Initially, 1:1 adducts were isolated. Decomposition of the adducts in refluxing benzene yielded 2-pyrroline derivatives **9** and **10**, respectively. Aqueous sodium hydroxide converted the primary adducts to pyrroles **7** and **8**.[3] We now describe facile cycloaddition reactions of **2a** and other less stable oxazolium 5-oxides (**2b** and **2c**), generated in solution by dehydrative cyclization from the *N*-acyl amino acid precursors **3**, with a variety of 1,4-quinones **4** to produce the desired 2*H*-isoindole-4,7-diones (**1**) in moderate yields.[4]

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## Results and Discussion

1,3-Dipolar cycloaddition reactions of oxazolium 5-oxides have been intensely studied,[5-13] notably by Huisgen and colleagues.[5-7] The mesoionic compounds were prepared by cyclodehydration of *N*-acyl amino acids with reagents such as acetic anhydride or dicyclohexylcarbodiimide. Since the N-substituted 2,4-diaryloxazolium 5-oxides are the only examples stable enough for isolation, less stable

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