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Quinone Imines with a Fused Azine Ring: III. Synthesis and Reactivity of 8-*p*-Tolylsulfonylimino-5,8-dihydroquinolin-5-one Derivatives

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Abstract—Unstable 8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one was generated by oxidation of the corresponding reduced form in acetic acid; it reacted *in situ* with hydrogen chloride and sodium *p*-toluenesulfinate to give the corresponding 6-substituted 5-hydroxy-8-aminoquinolines.

There are almost no published data on N-substituted 8-imino-5,8-dihydroquinolin-5-ones. An attempt was made to correlate antimalarial activity of 8-amino-6-methoxyquinolines with their ability to undergo oxidation to 8-imino-6-methoxy-5,8-dihydroquinolin-8-ones [1], though the corresponding quinoid metabolites were not isolated by independent synthesis [2] because of their instability. The only stable compound of this series, 6-(4-methoxyphenylamino)-8-(4-methoxyphenylimino)-5,8-dihydroquinolin-5-one was obtained by treatment of 6-piperidino-5,8-dihydroquinoline-5,8-dione with excess *p*-methoxyaniline in acetic acid [3].

In the preceding communications we reported on the reactivity of 8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one derivatives. We found that reactions of these compounds with nucleophilic reagents are governed by the tosylimino group rather than by the endocyclic nitrogen atom [4, 5]. In the present work we made an attempt to synthesize 8-arylsulfonylimino-5,8-dihydroquinolin-5-ones. The initial model compound, 8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (**I**), and its derivatives were synthesized following the reaction sequence shown in Scheme 1. The reaction of 8-nitroquinoline (**II**) with hydroxylamine hydrochloride in alcoholic alkali afforded 5-amino-8-nitroquinoline (**III**). The latter was converted into 5-hydroxy-8-nitroquinoline (**IV**) by alkaline hydrolysis according to a specially developed procedure. For this purpose, nitro compound **IV** was reduced to 8-amino-5-hydroxyquinoline dihydrochloride (**V**) with tin(II) chloride in hydrochloric acid. Compound **V** was treated with *p*-toluenesulfonyl chloride in methanol in the presence of 2 equiv of pyridine to obtain 8-*p*-tolylsulfonylamino-5-hydroxyquinoline hydrochloride (**VI**). Oxidation of tosyl derivative **VI** with (diacetoxy-λ^3-iodanyl)benzene in acetic acid in the presence of an equimolar amount of sodium acetate afforded quinone imine **I** as a dark green solid material which gradually dissolved in the reaction mixture, giving rise to a dark blue solution. We failed to isolate quinone imine **I** as individual substance. Nevertheless, by treatment of the reaction mixture at the moment of formation of quinone imine **I** precipitate with hydrochloric acid or sodium *p*-toluenesulfinate dihydrate we succeeded in isolating new compounds, 6-chloro-5-hydroxy-8-*p*-tolylsulfonylaminoquinoline hydrochloride (**VII**) and 5-hydroxy-6-*p*-tolylsulfonyl-8-*p*-tolylsulfonylaminoquinoline (**VIII**), respectively.

The presence of a substituent in position *6* of the quinoline ring system was proved as follows. The oxidation of salt **VII** with (diacetoxy-λ^3-iodanyl)benzene under the same conditions as in the generation of quinone imine **I** gave unstable 6-chloro-8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (**IX**) which was treated *in situ* with hydrochloric acid. As a result, initial compound **VII** was obtained.

Compound **VIII** was oxidized with (diacetoxy-λ^3-iodanyl)benzene in acetic acid to obtain 6-*p*-tolylsulfonyl-8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (**X**), and the latter was treated with sodium *p*-toluenesulfinate dihydrate. As a result, the corresponding 6,1-addition product was isolated, 5-hydroxy-6-*p*-tolylsulfonyl-8-bis(*p*-tolylsulfonyl)aminoquinoline (**XI**). The same product was synthesized by reaction of quinone imine **IX** with 2 equiv of sodium *p*-toluenesulfinate dihydrate. Quinone imine **X** is readily soluble in acetic acid. In order to raise the yield of tritosyl derivative **XI** we tested a procedure according

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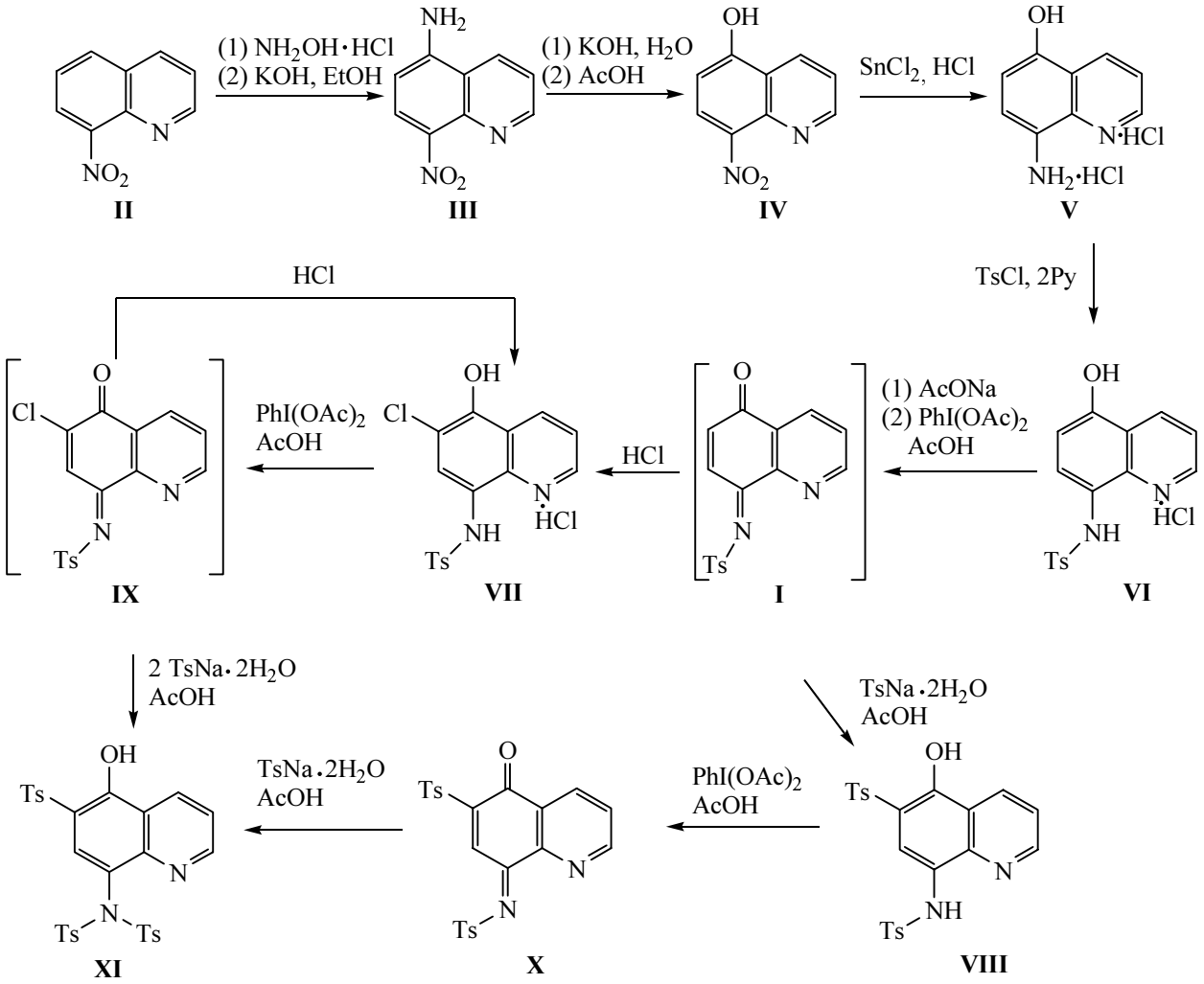
Scheme 1.



to which sodium *p*-toluenesulfinate dihydrate was directly added to the reaction mixture containing freshly prepared compound **X**.

The structure of the newly synthesized compounds was confirmed by their elemental analyses and ^{1}H NMR and IR spectra (see Experimental).

Our results led us to conclude that the endocyclic nitrogen atom (especially protonated) [3] and the arylsulfonylimino group consistently affect the reactions of 8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one with nucleophilic reagents. We believe that the vicinity of the endocyclic nitrogen atom possessing an unshared electron pair to the *p*-tolylsulfonylimino group (which increases the electron affinity of the quinoid ring) [6] is the main factor responsible for kinetic instability and enhanced reactivity of such quinone imines.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 instrument. The ^{1}H NMR spectra were obtained on a Varian VXR-200 spectrometer (199.9704 MHz) from 5% solutions in DMSO-d_6; the chemical shits were measured relative to tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using the following solvent systems: $CHCl_3$–CH_3OH–NH_3, 100 : 10 : 1 (**III**, **VI**, **VIII**, **XI**); 1-BuOH–H_2O–AcOH, 5 : 4 : 1 (**V**–**VII**); ethyl acetate (**X**); spots were visualized under UV light (**VI**–**VIII**, **XI**).

5-Amino-8-nitroquinoline (III). A hot solution of 20 g (0.30 mol) of 85% potassium hydroxide in 100 ml of ethanol was filtered and added dropwise to a suspension of 10.4 g (0.06 mol) of nitroquinoline **II** and 15 g

(0.22 mol) of hydroxylamine hydrochloride in 160 ml of ethanol under stirring at 40°C. The mixture was kept for 1 h at room temperature and poured onto 200 g of crushed ice. The precipitate was filtered off, washed with 20 ml of cold water, and dried at 60°C. Yield 6.3 g (55%), pale yellow powder, mp 248–50°C (from H_2O, decomp.); published data [7]: mp 252°C. ^{1}H NMR spectrum, δ, ppm: 6.65 d (1H, 6-H, J = 8.3 Hz), 8.16 d (1H, 7-H, J = 8.3 Hz), 7.51 d.d (1H, 3-H, J_1 = 4.3, J_2 = 8.3 Hz), 8.67 d.d (1H, 4-H, J_1 = 2.1, J_2 = 8.3 Hz), 8.94 d.d (1H, 2-H, J_1 = 2.1, J_2 = 4.3 Hz), 7.34 s (2H, NH_2).

5-Hydroxy-8-nitroquinoline (IV). A suspension of 1.1 g (5.8 mmol) of aminonitroquinoline **III** in 130 ml of water containing 1.1 g (20.0 mmol) of 85% potassium hydroxide was heated at the boiling point until it turned homogeneous and ammonia no longer evolved. The resulting hot solution was treated with charcoal and filtered, and the filtrate was acidified with acetic acid and cooled under stirring. The precipitate was filtered off, washed with 10 ml of water on a filter, and dried at 65–70°C. Yield 0.85 g (77%), orange finely crystalline substance, mp 260–261°C (decomp.); published data [8]: mp 258–261°C. ^{1}H NMR spectrum, δ, ppm: 6.81 d (1H, 6-H, J = 9.3 Hz), 8.23 d (1H, 7-H, J = 9.3 Hz), 7.61 d.d (1H, 3-H, J_1 = 4.8, J_2 = 8.2 Hz), 8.67 d.d (1H, 4-H, J_1 = 2.1, J_2 = 8.2 Hz), 8.96 d.d (1H, 2-H, J_1 = 2.1, J_2 = 4.8 Hz).

8-Amino-5-hydroxyquinoline dihydrochloride (V). Nitro compound **IV**, 12.3 g (0.065 mol), was added to a hot freshly prepared solution of tin(II) chloride in hydrochloric acid, which was prepared from 32 g (0.26 mol) of tin and 120 ml of concentrated hydrochloric acid. The mixture was stirred for 3 h on heating at the boiling point and was then kept for 24 h at room temperature. The precipitate was filtered off and dissolved in 600 ml of warm water, and a stream of hydrogen sulfide was passed through the solution while stirring. The mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from 17% hydrochloric acid to obtain 10.3 g (68%) of compound **V** as a lemon-yellow crystalline substance with mp 252–254°C (decomp.); published data [9]: mp 252–255°C.

5-Hydroxy-8-*p*-tolylsulfonylaminoquinoline hydrochloride (VI). A solution of 1.7 g (0.02 mol) of freshly distilled pyridine in 5 ml of methanol was added dropwise under stirring to a suspension of 2.3 g (0.01 mol) of dihydrochloride **V** and 1.9 g of *p*-toluenesulfonuyl chloride in 10 ml of methanol. The mixture was stirred for 30 min, and the precipitate was filtered off, washed with 10–15 ml of methanol, and dried. Yield 3.1 g (89%), lemon-yellow finely crystalline substance, mp 232–233.5°C (from acetic acid, decomp.). IR spectrum, ν, cm^{-1}: 1376, 1172 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 7.08 d (1H, 6-H, J = 8.7 Hz), 7.22 d (1H, 7-H, J = 8.7 Hz), 7.27 d (2H, C_6H_4, J = 8.8 Hz), 7.56 d (2H, C_6H_4, J = 8.8 Hz), 7.75 d.d (1H, 3-H, J_1 = 4.8, J_2 = 7.9 Hz), 8.87 d.d (1H, 4-H, J_1 = 2.2, J_2 = 7.9 Hz), 8.98 d.d (1H, 2-H, J_1 = 2.2, J_2 = 4.8 Hz), 9.89 s (1H, NH), 11.42 s (1H, OH). Found, %: N 7.89; S 9.07. $C_{16}H_{14}N_2O_3S \cdot HCl$. Calculated, %: N 7.98; S 9.14.

Generation of 8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (I) from hydrochloride VI. (Diacetoxy-λ^3-iodanyl)benzene, 1 g (3.1 mmol), was added to a suspension of 1.1 g (3.1 mmol) of salt **VI** and 0.26 g (3.1 mmol) of sodium acetate in 10 ml of glacial acetic acid, and the mixture was stirred for 10–15 min.

6-Chloro-5-hydroxy-8-*p*-tolylsulfonylaminoquinoline hydrochloride (VII). Concentrated hydrochloric acid, 3 ml, was added to a mixture containing quinone imine **I** (see above), and the mixture was stirred for 10 min. The precipitate was filtered off, washed on a filter with 5 ml of glacial acetic acid, thoroughly squeezed, and dried at 65–70°C. Yield 0.95 g (79% calculated on hydrochloride **VI**), brownish–yellow finely crystalline substance, mp 159–161°C (from acetic acid, decomp.). IR spectrum, ν, cm^{-1}: 1368, 1164 (SO_2); 3448 (NH, OH). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 7.54 s (1H, 7-H), 7.23 d (2H, C_6H_4, J = 8.8 Hz), 7.65 d (2H, C_6H_4, J = 8.8 Hz), 7.58 d.d (1H, 3-H, J_1 = 4.4, J_2 = 8.3 Hz), 8.55 d.d (1H, 4-H, J_1 = 2.6, J_2 = 8.3 Hz), 8.79 d.d (1H, 2-H, J_1 = 2.6, J_2 = 4.4 Hz), 9.83 s (1H, NH), 10.38 s (1H, OH). Found, %: N 7.22; S 8.26. $C_{16}H_{13}ClN_2O_3S \cdot HCl$. Calculated, %: N 7.27; S 8.32.

5-Hydroxy-6-*p*-tolylsulfonyl-8-*p*-tolylsulfonylaminoquinoline (VIII). Sodium *p*-toluenesulfinate dihydrate, 1.1 g (5.1 mmol), was added to a mixture containing quinone imine **I** (see above), and the mixture was stirred for 10 min. The precipitate was filtered off, washed with 10 ml of glacial acetic acid, squeezed, and dried at 65–70°C. Yield 1.2 g (82% calculated on hydrochloride **VI**), yellowish–pink finely crystalline substance, mp 219–220°C (from acetic acid, decomp.). IR spectrum, ν, cm^{-1}: 1339, 1172 (SO_2); 3240 (OH, NH). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, C**H**$_3$C$_6$H$_4$N), 2.33 s (3H, 4-C**H**$_3$C$_6$H$_4$SO$_2$C), 7.26 d (2H, CH$_3$C$_6$**H**$_4$SO$_2$C, J = 8.1 Hz), 7.38 d (2H, 4-CH$_3$C$_6$**H**$_4$SO$_2$N, J = 8.1 Hz), 7.65 d (2H, 4-CH$_3$C$_6$**H**$_4$SO$_2$N, J = 8.1 Hz), 7.74 d (2H,

4-$CH_3C_6\mathbf{H}_4SO_2C$, J = 8.1 Hz), 7.59 d.d (1H, 3-H, J_1 = 4.0, J_2 = 7.6 Hz), 8.04 s (1H, 7-H), 8.61 d.d (1H, 4-H, J_1 = 1.8, J_2 = 7.6 Hz), 8.88 d.d (1H, 2-H, J_1 = 1.8, J_2 = 4.0 Hz), 9.82 s (1H, NH), 11.15 s (1H, OH). Found, %: N 5.93; S 13.57. $C_{23}H_{20}N_2O_5S_2$. Calculated, %: N 5.98; S 13.69.

Generation of 6-chloro-8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (IX) from hydrochloride VII. (Diacetoxy-λ^3-iodanyl)benzene, 0.48 g (1.5 mmol), was added to a suspension of 0.6 g (1.5 mmol) of hydrochloride **VII** and 0.12 g (1.5 mmol) of sodium acetate in 3 ml of glacial acetic acid, and the mixture was stirred for 10–15 min.

Reduction of quinone imine IX with hydrogen chloride. Concentrated hydrochloric acid, 1.5 ml, was added to a mixture containing quinone imine **IX** (see above), and the mixture was stirred for 10 min. The precipitate was filtered off, washed with 3 ml of glacial acetic acid on a filter, thoroughly squeezed, and dried at 65–70°C. The product was recrystallized from acetic acid to obtain an orange–yellow finely crystalline substance which showed no depression of the melting point on mixing with hydrochloride **VII**.

6-*p*-Tolylsulfonyl-8-*p*-tolylsulfonylimino-5,8-dihydroquinolin-5-one (X). (Diacetoxy-λ^3-iodanyl)-benzene, 0.27 g (0.85 mmol), was added under stirring to a suspension of 0.4 g (0.85 mmol) of quinoline **VIII** in 3 ml of acetic acid. The mixture was stirred for 1 h, and the precipitate was filtered off, washed with acetic acid and hexane, and dried in air. Yield 0.3 g (77%), mustard-yellow needles with mp 224–225°C (from toluene, decomp.). The product is stable within a week since isolation. IR spectrum, ν, cm^{-1}: 1328, 1164 (SO_2); 1668 (C=O, C=N). ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, 4-C$\mathbf{H}_3C_6H_4SO_2C$), 2.38 s (6H, 4-C$\mathbf{H}_3C_6H_4SO_2N$), 7.34 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2C$, J = 8.1 Hz), 7.46 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2N$, J = 8.1 Hz), 7.69 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2N$, J = 8.1 Hz), 7.72 s (1H, 7-H), 7.62 d.d (1H, 3-H, J_1 = 5.4, J_2 = 8.1 Hz), 8.93 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2C$, J = 8.1 Hz), 8.28 d.d (1H, 4-H, J_1 = 2.2, J_2 = 8.1 Hz), 9.01 d.d (1H, 2-H, J_1 = 2.2, J_2 = 5.4 Hz). Found, %: N 5.93; S 13.68. $C_{23}H_{18}N_2O_5S_2$. Calculated, %: N 6.00; S 13.75.

5-Hydroxy-6-*p*-tolylsulfonyl-8-bis(*p*-tolylsulfonyl)aminoquinoline (XI). *a*. Sodium *p*-toluenesulfinate dihydrate, 0.5 g (2.3 mmol), was added to a mixture containing quinone imine **X** prepared from 0.4 g (0.85 mmol) of compound **VIII**, and the mixture was stirred for 10 min. The precipitate was filtered off, washed on a filter with 2 ml of glacial acetic acid, squeezed, and dried at 65–70°C. Yield 0.3 g (79% calculated on **VIII**), pale pink finely crystalline substance, mp 221–222°C (from acetic acid, decomp.).

b. Sodium *p*-toluenesulfinate dihydrate, 1.0 g (4.6 mmol), was added to a mixture containing quinone imine **IX**, and the mixture was stirred for 10 min. The product was isolated and purified as described above in *a*. Yield 0.7 g (76% calculated on hydrochloride **VII**), yellowish–pink finely crystalline substance, mp 220.5–222°C (decomp.). No depression of the melting point was observed on mixing with a sample prepared from quinone imine **X**. IR spectrum, ν, cm^{-1}: 1361, 1175 (SO_2); 3276 (OH). ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, 4-C$\mathbf{H}_3C_6H_4SO_2C$), 2.43 s (6H, 4-C$\mathbf{H}_3C_6H_4SO_2N$), 7.45 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2C$, J = 8.7 Hz), 7.45 d (4H, 4-$CH_3C_6\mathbf{H}_4SO_2N$, J = 8.7 Hz), 7.62 s (1H, 7-H), 7.58 d.d (1H, 3-H, J_1 = 4.9, J_2 = 8.6 Hz), 7.76 d (4H, 4-$CH_3C_6\mathbf{H}_4SO_2N$, J = 8.7 Hz), 7.76 d (2H, 4-$CH_3C_6\mathbf{H}_4SO_2C$, J = 8.7 Hz), 8.70 d.d (1H, 4-H, J_1 = 1.2, J_2 = 8.6 Hz), 8.79 d.d (1H, 2-H, J_1 = 1.2, J_2 = 4.9 Hz). Found, %: N 4.45; S 15.39. $C_{30}H_{26}N_2O_7S_3$. Calculated, %: N 4.50; S 15.45.

REFERENCES

1. Scönhöfer, F., *Z. Physiol. Chem*., 1942, vol. 274, p. 1; *Chem. Abstr*., 1943, vol. 37, p. 5064[5].
2. Pratt, Y.T. and Drake, N.L., *J. Am. Chem. Soc*., 1951, vol. 73, p. 544.
3. Chernyak, S.A. and Tsizin, Yu.S., *Zh. Org. Khim*., 1978, vol. 14, p. 1310.
4. Belov, A.V. and Nichvoloda, V.M., *Russ. J. Org. Chem*., 2004, vol. 40, p. 93.
5. Belov, A.V. and Nichvoloda, V.M., *Russ. J. Org. Chem*., 2004, vol. 40, p. 409.
6. Freimanis, Ya.F., *Izv. Akad. Nauk Latv. SSR, Ser. Khim*., 1986, p. 110.
7. Hasegawa, M. and Okamoto, T., *Yakugaku Zassi*, 1973, vol. 93, p. 1019; *Ref. Zh., Khim*., 1974, no. 5 Zh 315.
8. Fuson, R.C., Bauman, R.A., Howard, E., and Marvell, E.N., *J. Org. Chem*., 1947, vol. 12, p. 799.
9. Burckhalter, J.H., Edgerton, W.H., and Durden, J.A., *J. Am. Chem. Soc*., 1954, vol. 76, p. 6089.