# A NEW SYNTHESIS OF QUINOL-2,4-DIONES

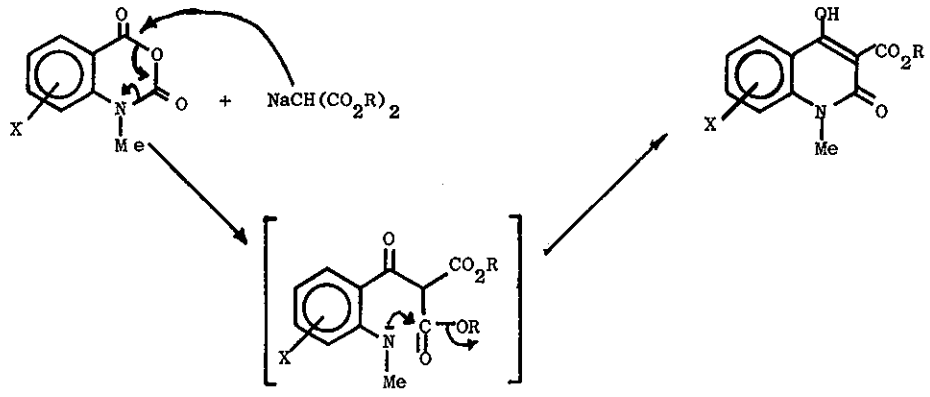
Lester A. Mitscher,* George W. Clark, Toshio Suzuki and
Mohindar S. Bathala**
Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas 66045

N-Methyl-3-(3-methyl-2-butenyl)-2,4-dihydroxyquinoline (4) has been synthesized by a new method involving the condensation of N-methylisatoic anhydride with diethylmalonate followed by alkylation with 4-bromo-2-methyl-2-butene and decarbethoxylation with copper (II) acetate in hot hexamethylphosphorous-triamide giving the desired quinol-2,4-dione system. Alternate procedures were studied and were found successful, but in lower yields. The new procedure represents a versatile entry into compounds of this type and promises to be general.

*To whom correspondence should be directed.

**Present address: Division of Pharmaceutics, The Ohio State University, Columbus, Ohio 43210

Because of the antimicrobial activity of pteleatinium chloride (1)[1], the wide distribution of quinol-2,4-diones in nature,[2] and a desire to be able to make analogs for biological testing, a flexible synthesis of 2,4-quinolones was sought. There are a number of existing syntheses of this sytem.[3] The most commonly used procedure, that of Grundon et al. (heating a substituted aniline with a 2-substituted malonate ester), requires a pyrolytic ring acylation in the quinoline ring-forming step. Although the procedure is short, it has the disadvantages of occasionally giving low yields and being susceptible to orientation problems when certain substituted anilines are employed. We therefore explored the use of N-methylisatoic anhydride as a starting material. This substance and its several commercially available analogs[4] have the advantage of having the desired aryl-carbonyl bond preformed. The concept of the new process is illustrated in the scheme:



In practice, treatment of N-methylisatoic anhydride (2) in refluxing glyme for 24 hr. with 2 equivalents of sodiodiethylmalonate afforded, after chromatography, N-methyl-3-carbethoxy-2,4-dihydroxyquinoline (3) in 55% yield. [m.p. 103-104°, pmr δ ($CDCl_3$): 1.47 (3H, t, J=7 Hz, $-CH_2\underline{CH}_3$), 3.61 (3H, s, NMe), 4.50 (2H, q, J=7 Hz, $-O\underline{CH}_2Me$), 7.00-8.30 (4H, m, ArH), 14.17 (1H, br.s, exchangable, -C=CO<u>H</u>)]. Alkylation of 3 in refluxing acetone with 4-bromo-2-methyl-2-butene and $K_2CO_3$ for 22 hr. gave N-methyl-3-(3-methyl-2-butene)-3-carbethoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (4) in 75% yield as a pale yellow oil. [i.r. 1760, 1696, 1663 and 1608 $cm^{-1}$, pmr δ ($CDCl_3$): 1.18 (3H, t, J=7 Hz, $-CH_2\underline{CH}_3$), 1.43 and 1.50 (3H each, br. s, $-CH=C\underline{Me}_2$), 3.07 (2H, br. d, J=7 Hz, $-\underline{CH}_2CH=$), 3.44 (3H, s, NMe), 4.18 (2H, t, J=7 Hz, $-\underline{CH}_2Me$), 4.85 (1H, br. t, J=7 Hz, $-\underline{CH}=CMe_2$), 7.00-8.30 (4H, m., ArH), eims† $M^+$=315]. Decarbethoxylation was carried out in hot (228°) hexamethylphosphoroustriamide for 1.5 hr. in the presence of copper (II) acetate.[5] After chromatography on silica gel, 5 was obtained in 67% yield. [m.p. 151-153°, i.r.3250-3450 $cm^{-1}$, 1638, 1616 and 1592 $cm^{-1}$, pmr δ ($CDCl_3$) 1.79 and 1.83 (3H each, br. s, $-CH=C\underline{Me}_2$),3.52 (2H br. d, J=7.5 Hz, $-\underline{CH}_2CH=CMe_2$), 3.68 (3H, s, NMe), 5.40 (1H, br. t, J=7.5 Hz, $-CH_2\underline{CH}=CMe_2$), 7.00-8.30 (4H, m, ArH), eims, $M^+$=243]. Conversion of 5 and its analogs to the pteleatinium system can be accomplished by the Grundon methods.[3]

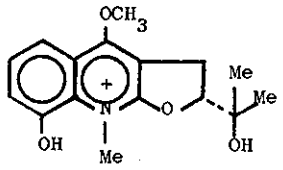
Some less satisfactory but still successful variations on this basic route were also investigated. Acid 6 was obtained in

---

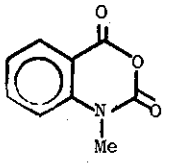
†electron impact mass spectrometry.

90% yield by treatment (3 hr, room temp.) of 3 with $BBr_3$ in chloroform. [m.p. 190-191°, pmr δ($CDCl_3$): 3.74 (3H, s, NMe), 7.23-8.45 (4H, m, ArH), 14.56 and 15.53 (1H each, s, $-CO_2\underline{H}$ and $O\underline{H}$, both exchangable), eims, $M^+$= 219, anal. C, H, N]. Reaction of 6 with 2,2,2-trichloroethanol and dicyclohexylcarbodiimide in refluxing benzene (23 hr) afforded trichloroester 7 in 58% yield. [m.p. 128-129°, ir 1668, 1660, 1650 and 1636 $cm^{-1}$, pmr δ ($CDCl_3$): 5.83 (2H, s, $-OC\underline{H}_2CCl_3$), eims, $M^+$=349, anal. C, H, N]. Alkylation of 7 was carried out in refluxing acetone (48 hr) with 4-bromo-2-methyl-2-butene and $K_2CO_3$. After chromatography, 8 was obtained as an oil in only 18% yield. [i.r. 1775, 1697, 1662 and 1605 $cm^{-1}$, pmr δ($CDCl_3$) 1.47 and 1.54 (3H each, s, $-CH=C\underline{Me}_2$), 3.13 (2H, br. d, J=7.5 Hz, $-C\underline{H}_2CH=CMe_2$), 3.48 (3H, s, NMe), 4.72 (2H, s, $-OC\underline{H}_2CCl_3$), 4.89 (1H, br. t, J=7.5 Hz, $-CH_2C\underline{H}=CMe_2$), 7.00-8.10 (4H, m, ArH), eims $M^+$=417]. Conversion of 8 to 5 was accomplished in 97% yield by treatment with zinc dust in acetic acid for 10 mins.

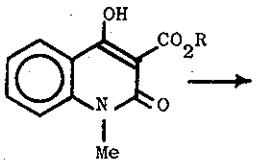
The low yield in the alkylation step spoiled that process. This is attributable to formation of substantial quantities (76%) of dialkylated product 9. [i.r. 1693, 1660 and 1605 $cm^{-1}$, pmr δ ($CDCl_3$) 1.48 and 1.57 (6H each, s, 2 x $CH=C\underline{Me}_2$), 2.70 (4H, br. d, J=7.5 Hz, 2 x $-C\underline{H}_2CH=CMe_2$), 3.43 (3H, s, NMe), 4.83 (2H, br. t, J=7.5 Hz, 2 x $-CH_2C\underline{H}=CMe_2$), 6.95-8.10 (4H, m, ArH), eims $M^+$=311]. The mechanism of the formation of 9 from 8 is unclear. Detrichloroethoxylation of 8 is, however, a very facile process. Hydrolysis of 3 occurs very readily (heating at 138° for 30 mins



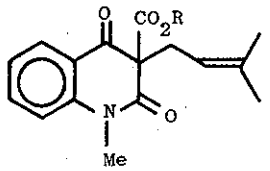
(1)



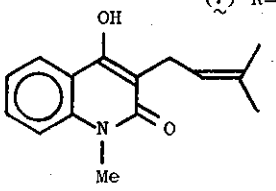
(2)



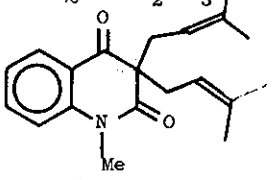
(3) R=Et
(6) R=H
(7) R=$CH_2CCl_3$



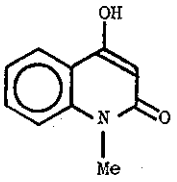
(4) R=Et
(8) R=$CH_2CCl_3$



(5)



(9)



(10)

in glycerol containing a trace of water)[6] to give N-methyl-quinol-2,4-dione (10) in 77% yield. [m.p. above 260°, pmr δ ($CDCl_3$ + DMSO-$d_6$): 3.64 (3H, s, NMe), 6.63 (1H, s, $C_3H$), 7.17-8.13 (4H, m, ArH), eims $M^+$=161]. On the other hand, compound 4 failed to give 5 (starting material is recovered in excellent yield even upon heating in glycerol at 220°). It seems plausible that the alkaline alkylating conditions cause hydrolysis and decarboxylation of 8 followed by alkylation again to 9. Alternately, deesterification-decarboxylation to 10 followed by bisalkylation (a reaction we have observed separately) is alternately possible. In fact, attempted monoalkylation of 10 fails in our hands due to predominate formation of 9. Others have made similar observations.[7] This may also be overcome by monobromination of 10 followed by alkylation and removal of the halogen with zinc dust to give 5 in good yield. Unusual hydrolytic conditions were explored because of the extensive cleavage to undesirable side products that 4 undergoes using conventional alkaline and acidic hydrolysis conditions.

ACKNOWLEDGEMENT. The authors thank the NIH for financial support of this work under grant number AI09846-06.

REFERENCES

1. L. A. Mitscher, M. S. Bathala, G. W. Clark and J. L. Beal, Lloydia, 38, 109, 117 (1975); L. A. Mitscher, M. S. Bathala and J. L. Beal, Chem. Commun., 1040 (1971).
2. D. L. Dreyer, Phytochemistry, 8, 1013 (1969); V. L. Bailey and H. E. Bailey, Brittonia, 22, 346 (1970); J. R. Price, Prog Chem. Org. Nat.Prod., 13, 317 (1956); H. G. Boit, Ergebnisse der Alkaloid-Chemie bis 1960, Acadamie-Verlag, Berlin, p. 716 (1961).

3. J. F. Collins, G. A. Gray, M. F. Grundon and D. A. Harrison, J. Chem. Soc., Perkin Trans. I, 94 (1973); Y. Kurayama, T. Ota, T. Mikata and H. Kanda, Yakugaku Zasshi, 88, 1050 (1968); H. Tuppy and F. Böhm, Monats. Chem., 87, 721 (1956); S. Prabhakas, B. R. Pai and V. N. Ramachandran, Indian J. Chem., 9, 191 (1971); R. G. Cooke and H. F. Haynes, Austr. J. Chem., 11, 225 (1958).

4. K and K Rare Chemicals, Aldrich Chemical Company, Pfalts and Bauer, and The Sherwin Williams Chemical Company.

5. T. Kametani, T. Susuki, K. Takahashi and K. Fukumoto, Synthesis, 2, 131 (1974).

6. N. J. Toivonen, S. Niininen, S. Eskola, P. V. Laakso and P. Laukkanen, Acta Chem. Scand., 1, 133 (1947). We are pleased to acknowledge Professor G. Fodor (U. of West Virginia) for bringing this article to our attention.

7. For example, see P. Venturella, A. Bellino and F. Piozzi, Heterocycles, 3, 367 (1975).

Received, 22nd August, 1975