acid, or with sodium methoxide in anhydrous methanol, resulted only in recovery of starting material in high yield.

Octadecylamine gave 2-chloro-3-octadecylamino-1,4-naphthoquinone, m. p. 97–98°. Calcd. for $C_{28}H_{42}O_2NCl$: N, 3.04. Found: N, 3.21. Hydrolysis of this material took a similar course.

Summary

1. Mannich bases have been prepared from lawsone, higher primary aliphatic amines and, as the aldehyde component, formaldehyde, benzaldehyde, or acetaldehyde. Higher secondary aliphatic amines give rise to salts of methylene-bis-lawsone. A mechanism for these reactions is suggested.

2. 2,5-Dihydroxy-1,4-benzoquinone also takes part in the Mannich reaction.

3. The Mannich bases cannot be used as alkylating agents.

4. Some 3-alkylamino-1,4-naphthoquinones and their reactions are described.

5. The compounds prepared are devoid of significant antimalarial activity.

CAMBRIDGE 38, MASS. RECEIVED OCTOBER 11, 1948

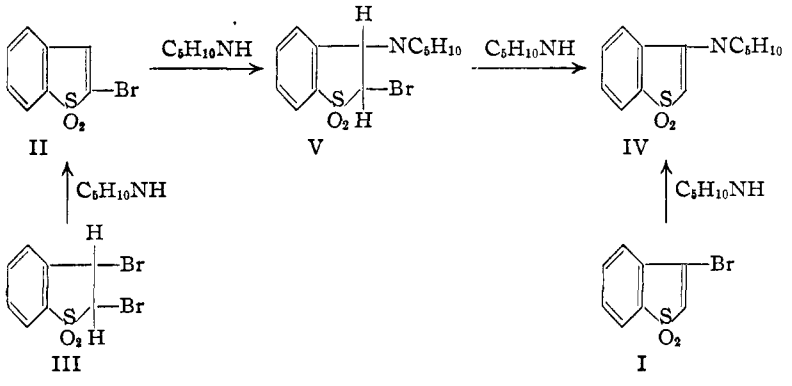
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Thianaphthene Chemistry. III. The Reaction of 2,3-Dibromo-2,3-dihydro- and 2-Bromo-thianaphthene-1-dioxides with Secondary Amines

BY F. G. BORDWELL, B. B. LAMPERT AND W. H. MCKELLIN

In a previous paper[1] the bromine atom in 3-bromothianaphthene-1-dioxide (I) was shown to be readily replaced in reactions with primary and secondary aliphatic amines or with alkoxides. It seemed of interest to test the reactivity of the isomeric 2-bromo-thianaphthene-1-dioxide (II) under similar conditions.

Thianaphthene was oxidized with hydrogen peroxide or peracetic acid in acetic acid solution to give thianaphthene-1-dioxide in greater than 90% yield. The dioxide did not react noticeably with bromine in carbon tetrachloride solution except under the influence of ultraviolet light, whereby a slow reaction occurred to give 2,3-dibromo - 2,3 - dihydrothianaphthene - 1 - dioxide (III). In hot acetic acid solution the addition was effected without illumination. The product



from the latter reaction was the same as that obtained from the reaction in carbon tetrachloride, so apparently addition of bromine to thianaphthene-1-dioxide by a free radical or ionic mechanism followed the same steric course (presumably *trans* addition). Refluxing III in benzene or alcohol solution with excess pyridine gave a quantitative yield of 2-bromothianaphthene-1-dioxide (II).

None of the bromine in I and II was released by boiling with aqueous or alcoholic silver nitrate solutions for four hours. The inertness of these bromides toward electrophilic attack by silver ion (S_N1 mechanism) is not surprising in view of the electron-attracting properties of the sulfonyl group. The addition of a small amount of sodium hydroxide to the solution of the bromide caused the rapid release of bromide ion in each case. It was found that II reacted rapidly with piperidine in hot benzene solution with the precipitation of piperidinium bromide. The bromine in II was not directly replaced by a piperidino group in this reaction, however, as was the case for I.[1] Instead, the product of the reaction was found to be 3-(1-piperidino)-thianaphthene-1-dioxide (IV), identical with the product obtained from the reaction of I with piperidine. Morpholine reacted with II in an analogous manner to give 3-(N-morpholino)-thianaphthene-1-dioxide, identical with the product obtained from I and morpholine. Similarly sodium methoxide in methyl alcohol solution gave 3-methoxythianaphthene-1-dioxide. Diethylamine did not appear to react under similar conditions, II being recovered for the most part from the reaction mixture (I reacts readily with diethylamine[1]). It seemed likely that the reaction of II with piperidine, morpholine and sodium methoxide proceeded by addition of the amine or alcohol to the 2,3-double bond to give an addition product (V) followed by dehydrobromination to IV, as shown for piperidine ($C_5H_{10}NH$).

Further investigation showed that V, as well as IV, was present in reaction mixtures in which

(1) Bordwell and Albisetti, THIS JOURNAL, 70, 1558 (1948); for paper II see, *ibid.*, 70, 1955 (1948).

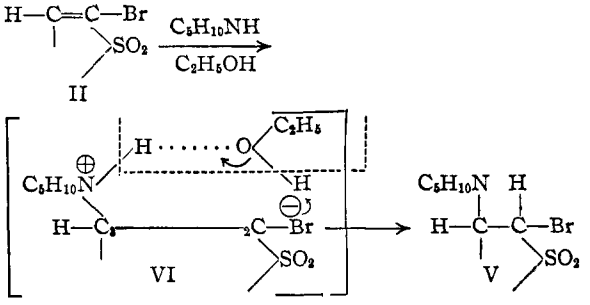
II and excess piperidine had been allowed to react for one and one-half hours in refluxing benzene solution. At room temperature II with piperidine in alcohol solution gave over 90% of V in one hour. Morpholine and diethylamine reacted in an analogous manner but at slower rates. Dehydrobromination of V was effected by use of piperidine in refluxing alcohol solution confirming the possibility of forming IV from II by way of V as shown in the equations.

In order to gain further information concerning the manner and rate of formation of IV from II, V and also III, the amount of bromide ion released from these bromides in various time intervals in the reaction with excess piperidine in refluxing benzene and alcohol solutions was determined. Similar determinations were made on reactions using morpholine and diethylamine. Where it seemed desirable, a product analysis was made in conjunction with the quantitative determination. The molar ratios of amine to bromide used were: 5/1 for V and its analogs; 6/1 for II; and 7/1 for III.

The quantitative study showed that in the reaction with piperidine in refluxing benzene solution the release of bromide ion was about five to six times as great from II as from V in one-half hour (60, 58% *vs.* 14, 10%). Clearly V cannot be a primary intermediate in this reaction and the simple mechanism illustrated by the equations for the formation of IV from II is not the only course possible for this transformation. The reactions of the morpholino and diethylamino analogs of V under comparable conditions with morpholine and diethylamine, respectively, released 18 and 12% of bromide ion in two hours as compared to 28% from II and morpholine and 9% from II and diethylamine.

In refluxing alcohol solution the release of bromide ion from II in the reaction with piperidine was considerably slower than in benzene solution, 19–26% (six determinations) of bromide ion being released in one-half hour. The difference is accounted for by the greater rapidity of the addition reaction in alcohol solution. Thus, 91% of V was isolated from the reaction of II with piperidine after five minutes in refluxing alcohol solution, whereas more than 60% of II was recovered from a similar experiment in benzene solution. With V and piperidine in refluxing alcohol solution 10–14% (two determinations) of bromide ion was released in one-half hour. With diethylamine, the diethylamino analog of V released 8% of bromide ion in two hours as compared to 6% from II. The reactions in alcohol solution appear to proceed principally by the mechanism outlined in the equations.

Thus far we have been unsuccessful in our attempts to formulate a satisfactory mechanism for the reaction in benzene solution whereby II goes to IV without involving V as an intermediate. The most logical initial step for the reaction between II and piperidine would appear to be formation of an intermediate addition complex such as VI. The conversion of VI to V requires only the transfer of a proton from the nitrogen to the carbon bearing the negative charge. In alcohol and similar solvents this may be accomplished by means of a solvent bridge involving hydrogen bonding, as shown in the diagram, or by a Lowry mechanism utilizing several solvent molecules. In benzene solution the role of the solvent must be played by piperidine or the proton transfer made directly, so it is not surprising that the addition is slower. The formation of IV directly from VI would require the release of bromide ion and a proton from the 3-carbon atom to be simultaneous with, or precede, the proton transfer pictured above. Such a process is difficult to rationalize.[2]

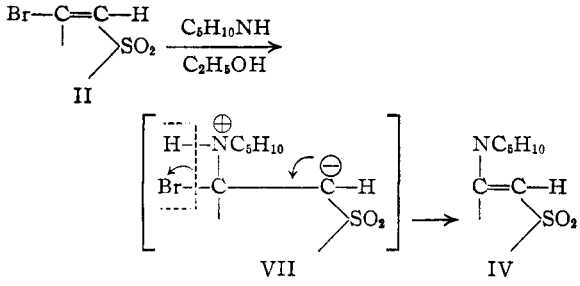


Under the conditions in alcohol solution where II released 19–26% of bromide ion in the reaction with piperidine the release of bromide ion from I was quantitative. Attempts to isolate an addition product from the reaction of I with piperidine under conditions similar to those used for the isolation of V were unsuccessful. These results are understandable since the addition complex VII, unlike the addition complex VI, may readily form IV by release of bromide ion and a proton.[3]

The reaction of III with the amines proceeded in two stages. Release of the first equivalent of bromide ion was very rapid in alcohol or benzene solution, being complete within five minutes when piperidine was used. In benzene solution this

(2) Cromwell, *et al.*, *Chem. Rev.*, **38**, 83 (1946), have shown that certain α-bromo-β-dialkylaminoketones readily form three-membered cyclic imonium bromides. It is possible that similar compounds are formed in the conversion of V to IV, but we have no experimental evidence to suggest this course for the reaction. It is difficult to visualize a mechanism whereby II could be converted to a cyclic imonium ion without V as an intermediate, so postulation of this path for the reaction does not aid in interpreting our experimental results. Dr. F. N. Hayes has pointed out that it is possible to explain the more rapid conversion of II to IV than V to IV in benzene solution by assuming that a stereoisomer of V, which is more readily dehydrobrominated, is an intermediate in the former reaction.

(3) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1257 (1937), have classified displacement reactions of aryl halides with those of alkyl halides by assuming that addition complexes, such as VII, from aryl halides are comparable to the transition states, $R_3N\cdots R\cdots X$, written for the S_N2-type reactions of alkyl halides. Such simplification is, no doubt, desirable but it should be kept in mind that there are some differences in the two reaction types. For example, aryl chlorides and bromides react at comparable rates whereas alkyl chlorides and bromides do not.



reaction was dehydrobromination to give II, since the latter was isolated in high yield under these conditions. In alcohol solution the product was V, but the addition of piperidine to II is so rapid in alcohol that the initial reaction could still be dehydrobromination. It is possible that in alcohol V was formed by a direct replacement reaction, but this seems unlikely since when morpholine, which adds only slowly to II, was used the product was again II. The release of the second equivalent of bromide ion from III paralleled that from II under comparable conditions in reactions with piperidine, morpholine and diethylamine. The very rapid dehydrobromination of III is of interest since the hydrogen and bromine atoms are probably *cis*. In other instances it appears that *cis* dehydrohalogenation is a relatively slow reaction.[4]

It is a noteworthy commentary of the complexity of organic reactions that four different bromides (I, II, III, V) in reacting with piperidine may form the same product (IV) by at least three different mechanisms.

Acknowledgment.—This work was supported by a grant from the Abbott Fund of Northwestern University.

Experimental[5]

Thianaphthene-1-dioxide.—Lanfry[6] reported a 35% yield of this compound by oxidation of thianaphthene with excess hydrogen peroxide in dilute acetic acid. In the present investigation it was found that using three times the calculated amounts of 30% hydrogen peroxide (in acetic acid or acetic acid–acetic anhydride solution) or 20% peracetic acid gave over 90% yield of the desired product after heating for fifteen minutes at the reflux temperature. Comparable results were obtained with twice the calculated quantity of 90% hydrogen peroxide[7] in acetic acid containing ten drops of sulfuric acid (7.5 cc. of 90% peroxide, 100 cc. of acetic acid and 10 g. of thianaphthene) after three hours at 12°. When peracetic acid or 30% hydrogen peroxide in the presence of acetic anhydride was used a vigorous exothermic reaction occurred on warming the solution. The use of 30% hydrogen peroxide in acetic acid solution was most convenient.

A solution consisting of 10 g. (0.075 mole) of thianaphthene,[8] 60 cc. of acetic acid and 45 cc. (0.45 mole) of 30% hydrogen peroxide was refluxed for fifteen minutes and 200 cc. of water was added. After cooling 10.5 g. (85%) of thianaphthene-1-dioxide, m. p. 142–143°, was collected. Concentration of the solution gave additional quantities of product of comparable purity, the total yield being usually about 95%. Use of only 10% excess of hydrogen peroxide gave a lower yield of product. Crystallization from water or dilute alcohol gave a colorless product, m. p. 142–143°, which is the melting point reported by Lanfry.[6]

2,3-Dibromo-2,3-dihydrothianaphthene-1-dioxide (III).—A solution of 8.0 g. (0.05 mole) of bromine and 8.0 g. (0.048 mole) of thianaphthene-1-dioxide in 200 cc. of carbon tetrachloride was illuminated with a mercury arc lamp. Decolorization required two hours when a Vycor flask was used, six hours using a Pyrex flask. The dioxide dissolved during this time and the dibromide crystallized out. The total yield of dibromide, m. p. 166–168°, was quantitative. In acetic acid solution the reaction was carried out in the dark at 100°, and was complete within two hours to give a 71% yield of material m. p. 162–165°. The reaction was also run in aqueous solution at 100°, but the product was contaminated with 2-bromothianaphthene-1-dioxide (II), formed by dehydrobromination.

Lanfry[6] reported this compound but gave no experimental conditions for its preparation. Crystallization from water, as suggested by Lanfry,[6] led to impure material due to dehydrobromination to II; alcohol was found to be a much better solvent.

2-Bromothianaphthene-1-dioxide (II).—Heating benzene or alcohol solutions of III with a slight excess of pyridine resulted in rapid dehydrobromination. The reaction was quantitative in less than one hour. Recrystallization from water or alcohol gave colorless needles melting at 150–151°.

Anal. Calcd. for $C_8H_5O_2SBr$: C, 39.20; H, 2.06. Found: C, 39.37; H, 2.08.

The dehydrobromination was accomplished as well using triethylamine, aniline or 2-aminopyrimidine as the base. The reaction of III with morpholine in alcohol solution gave II after one hour at room temperature.

The Reaction of II with Piperidine.—A solution of 0.5 g. (0.002 mole) of II and 1.04 g. (0.012 mole) of piperidine in 20 cc. of dry benzene was heated to boiling. The separation of piperidinium bromide began after about fifteen minutes. At the end of one and one-half hours water was added. The residue from evaporation of the benzene layer was crystallized from alcohol. The first crop of crystals consisted of 0.25 g. (50%) of 3-(1-piperidino)-thianaphthene-1-dioxide (IV), m. p. 240°, the m. p. of which was not depressed by admixture with a pure sample, m. p. 246°, of this compound.[1] The second crop (0.2 g.) melted over a wide range, but on further crystallization gave 0.14 g. (21%) of **3-(1-piperidino)-2-bromo-2,3-dihydrothianaphthene-1-dioxide (V)**, m. p. 137–140°. An analytical sample of V prepared by crystallization from alcohol melted at 139–140°.

Anal. Calcd. for $C_{13}H_{16}O_2SBr$: N, 4.24. Found: N, 4.04.

The preparation of V was accomplished from either II or III and excess piperidine by reaction in alcohol solution for five minutes at the reflux temperature or one hour at room temperature. Dilution of the solution gave over 90% yield of V in every case. In benzene solution at the reflux temperature II gave but little reaction with excess piperidine in five minutes; after one hour at room temperature 15% of V and 65% of II were isolated; after twenty-four hours at room temperature 35% of V and 50% of IV were isolated.

3-Methoxythianaphthene-1-dioxide.—A solution of 0.5 g. (0.002 mole) of II and 0.12 g. (0.002 mole) of potassium hydroxide in methyl alcohol was refluxed for two and one-half hours. Removal of the solvent gave over 90% of crude product, which, after crystallization, melted at 218–220°, and did not depress the melting point of an authentic sample.[1]

The Reaction of 3-Bromothianaphthene-1-dioxide (I) with Piperidine and Morpholine.—Attempts to obtain an

(4) Cristol, THIS JOURNAL, **69**, 338 (1947).

(5) Microanalyses were by Misses Patricia Craig, Rosalyn Guy and Virginia Hobbs.

(6) Lanfry, *Compt. rend.*, **154**, 519 (1912).

(7) We are indebted to the Buffalo Electro-Chemical Company, Inc., Buffalo, New York, for furnishing 40% peracetic acid and 90% hydrogen peroxide.

(8) We wish to thank the Jefferson Chemical Company, Inc., New York, N. Y., for a generous supply of thianaphthene.

addition product from I and piperidine under the conditions used for II were unsuccessful; the only product isolated was IV. The reaction of I with morpholine was carried out as previously described for piperidine,[1] except that the reaction time was shortened to five minutes. The yield was nearly quantitative. A sample of **3-(N-morpholino)-thianaphthene-1-dioxide** crystallized from dilute alcohol and benzene–Skellysolve "B" was light yellow in color and melted at 222–223° (dec.).

Anal. Calcd. for $C_{12}H_{11}O_3NS$: N, 5.57. Found: N, 5.49.

3-(N-Morpholino)-2-bromo-2,3-dihydrothianaphthene-1-dioxide.—The morpholino analog of V was prepared from II in alcohol solution under conditions similar to those used for V, except that a longer time was required. At the end of six hours II was still present in appreciable quantities; after thirty-six hours a 92% yield of product was obtained. Crystallization from dilute alcohol gave colorless plates, m. p. 156–157°.

Anal. Calcd. for $C_{12}H_{14}NSBr$: N, 4.21. Found: N, 4.10.

After four hours at 80° in benzene solution using a 6:1 molar ratio of amine to II, 50% of 3-(N-morpholino)-2-bromo-2,3-dihydrothianaphthene-1-dioxide and 16% of 3-(N-morpholino)-thianaphthene-1-dioxide were isolated.

3-Diethylamino-2-bromo-2,3-dihydrothianaphthene-1-dioxide.—The addition of diethylamine to II in alcohol solution was carried out in a manner similar to that used above except that the solution had to be warmed at intervals to redissolve the starting material. At the end of twelve days a 68% yield of the product was obtained. Crystallization from dilute alcohol gave colorless plates, m. p. 88–88.5°.

Anal. Calcd. for $C_{12}H_{16}O_2NSBr$: N, 4.40. Found: N, 4.15.

It is interesting that the addition compounds (V and its analogs) are colorless whereas the corresponding unsaturated compounds (IV and its analogs) are yellow.

Quantitative Determinations.—The liberated bromide ion was determined by the Volhard titration method. In alcohol the titration was run directly on the reaction mixture. When benzene was used as a solvent, the reaction mixture was diluted with water and the water layer was either separated and the determination made on aliquots of the combined water layer and washings, or the total sample was titrated without separation of the layers. The latter method was simpler and gave better results.

Summary

The reaction of 2,3-dibromo-2,3-dihydrothianaphthene-1-dioxide (III) with excess piperidine may be conducted so as to yield 2-bromothianaphthene-1-dioxide (II), 2-bromo-3-(1-piperidino)-2,3-dihydrothianaphthene-1-dioxide (V) or 3-(1-piperidino)-thianaphthene-1-dioxide (IV).

Any one of these three products may be obtained in high yield if the solvent (benzene or alcohol), time and temperature are properly chosen. It is possible also to obtain IV and V from II, and to obtain IV from V.

A study of the quantity of bromide ion released from II, III, V and also 3-bromothianaphthene-1-dioxide (I) in the reaction with excess piperidine in benzene and alcohol solutions has been made. The mechanism of these reactions has been discussed in the light of this information.

EVANSTON, ILLINOIS RECEIVED SEPTEMBER 10, 1948

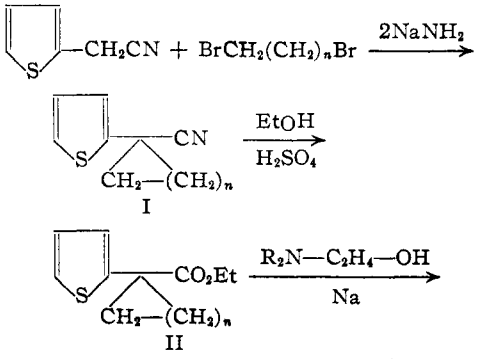
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

Aminoesters of 1-Substituted Alicyclic Carboxylic Acids[1]

BY CHARLES H. TILFORD, LEWIS A. DOERLE, M. G. VAN CAMPEN, JR., AND ROBERT S. SHELTON

The high spasmolytic activity of β-diethylaminoethyl 1-phenyl- and 1-cyclohexyl-cycloalkanecarboxylates has been previously reported.[2,3] More recently β-diethylaminoethyl 1-methylcyclohexanecarboxylate was investigated[4] as a spasmolytic agent. Further search has now led to the preparation of aminoesters of 1-(2-thienyl)-cycloalkanecarboxylic and 1-alkyl-cyclohexanecarboxylic acids. 1-Methyl-,[5] 1-ethyl-,[6] and 1-(*i*-propyl)-[7]cyclohexanecarboxylic acids and 1-methyl-,[8] 1-ethyl-,[9] and 1-propyl-cyclopentanecarboxylic[10] acids have been previously prepared. The most practical method reported[8] was the conversion of 1-methylcyclopentanol, obtained from cyclopentanone and methylmagnesium halide, to the corresponding chloride, which was converted to the Grignard reagent and allowed to react with carbon dioxide. Low yields of desired product are reported for the last two reactions.

The thienyl derivatives of the present study were prepared from thenyl cyanide and the appropriate alkylene dihalide in the presence of sodamide.[3]



(1) Presented at the 114th Meeting of the American Chemical Society, Medicinal Section, Washington, August 31, 1948.

(2) (a) Rubin and Wishinsky, THIS JOURNAL, **68**, 829 (1946); (b) Weston, *ibid.*, **68**, 2347 (1946); see U. S. Patent 2,404,588.

(3) Tilford, Van Campen and Shelton, *ibid.*, **69**, 2902 (1947).

(4) Levy and Tchoubar, *Compt. rend. soc. biol.*, **141**, 257 (1947).

(5) Tarbouriech, *Compt. rend.*, **150**, 1606–1607 (1910); Reichstein, *et al.*, *Helv. Chim. Acta*, **18**, 724 (1935); see also Gutt, *Ber.*, **40**, 2069 (1907); Meerwein, *Ann.*, **396**, 235 (1913).

(6) Meerwein, *Ann.*, **419**, 168 (1919); Arnold and Liggett, THIS JOURNAL, **64**, 2875–2877 (1942); German Patent 620,903.

(7) Shive, Crouch and Lochte, THIS JOURNAL, **63**, 2979 (1941).

(8) Meerwein, *Ann.*, **405**, 171 (1914); **417**, 263 (1918); Petrov, *J. Russ. Phys.-Chem. Soc.*, **45**, 644 (1912).

(9) Meerwein, *Ann.*, **396**, 230 (1913); **419**, 121–175 (1919).

(10) Meerwein, *ibid.*, **419**, 165 (1919).