Summary

The 1-(β,4-morpholine-ethyl) derivatives of barbital and amytal have been prepared. The former has been found ineffective as a hypnotic.

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[CONTRIBUTION FROM CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

The Autoxidation of Quininone[1]

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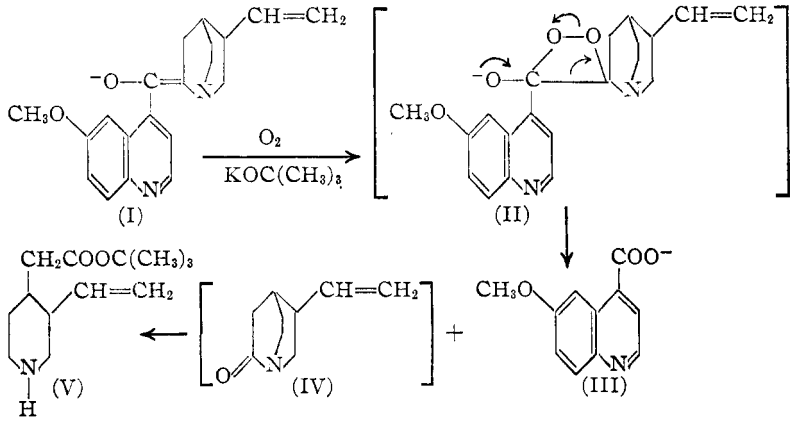
In the course of several experiments in which quininone was handled as its sodium or potassium derivative (I), we observed the occasional formation of quininic acid (III) in variable amounts. Woodward[2] suggested that the acid had been formed by the action of air on the enolate ion from quininone, and was able to isolate 50% of the theoretical amount of quininic acid and 10% of unchanged quininone from a reaction mixture obtained by passing air for three hours through a boiling solution of potassium enolate in benzene.[3]



In following up our initial observations, we have found that under certain conditions the oxidative cleavage of quininone is very rapid, and have been able to ascertain the fate of both halves of the original molecule. When a solution of quininone in *t*-butyl alcohol is shaken at room temperature with oxygen under two atmospheres pressure, the absorption of one mole of oxygen is complete in two to five minutes, the reddish orange color of the enolate being discharged and the temperature of the solution rising about twenty degrees. Quininic acid is isolated in 92% of the theoretical amount and identified by conversion to its methyl ester.

The other fragment from the cleavage of quininone has been found to be meroquinene *t*-butyl ester (V) isolated in 58% of the theoretical amount. The structure of the liquid ester follows from several observations. Analysis and titration confirm the empirical formula. A positive reaction with nitrous acid demonstrates the presence of a secondary amino group. Hydrolysis with acid gives meroquinene, and transesterification with ethanol forms the ethyl ester of meroquinene, identified as its hydrochloride.

The remarkable rate of the autoxidation is due to the presence of tertiary butoxide ion.[4] In neutral *t*-butyl alcohol, quininone is stable to oxygen, 70% of the starting material being recovered after shaking for a week, whereas in the presence of added potassium *t*-butoxide, quininone is oxidized completely in a few minutes. The difference in behavior may be ascribed to the fact that quininone is present in potassium *t*-butoxide solution as its potassium salt (I) and that this resonating anion is oxidized much more rapidly than either the keto or the enol form of quininone.[5]

The literature contains isolated references to the autoxidation of ketones. A majority of autoxidative cleavages we have been able to find involve the neutral compound and require either long periods of time or high temperatures or both for completion.[6,7] Kohler[6] has shown that the enol is oxidized a great deal more rapidly than the ketone. In several other examples in which alkali was present during the oxidation, it was not stated whether alkali accelerated the reaction or not.[8]

(1) The work was carried out under Government Contract WPB-191 between the Office of Production Research and Development and the Division of War Research, Columbia University.

(2) Woodward, private communication.

(3) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945)

(4) The role of peroxide catalysts in the reaction has been acknowledgedly left uninvestigated.

(5) The difference is the more surprising since quininone alone shows mutarotation and is therefore in labile equilibrium with the enol form.

(6) Kohler, *Am. Chem. J.*, **36**, 177 (1906); Kohler and Thompson, THIS JOURNAL, **59**, 887 (1937).

(7) Fortey, *J. Chem. Soc.*, **75**, 871 (1899); Salway and Kipping, *ibid.*, **95**, 166 (1909); Fuson, Byers and Rabjohn, THIS JOURNAL, **63**, 2639 (1941); Fuson, Maynert and Shenk, *ibid.*, **67**, 1939 (1945); Fleming, German Patent 583,704, Sept. 12, 1933; German Patent 597,973, June 2, 1934; Becker, German Patent 732,236, Jan. 28, 1943; Prückner, U. S. Patent 2,341,288, Feb. 8, 1944.

(8) Zinin, *Chem. Zentr.*, **42**, 211 (1871); Miller and Rohde, *Ber.*, **25**, 2095 (1892); Bogdanowska, *ibid.*, **25**, 1271 (1892); Graebe and Gfeller, *Ann.*, **276**, 12 (1893); Graebe and Jequier, *ibid.*, **290**, 199 (1896).

In three examples, the phase reaction of chlorophyll derivatives,[9] the oxidation of an α-diketone,[10] and the oxidation of benzoin methyl ether,[11] the accelerating action of alkali on the autoxidation of ketones was clearly exemplified. We are investigating the generality of the base-catalyzed autoxidation of carbonyl compounds.

The course of the autoxidation of quininone is probably similar to that of the examples cited above. Kohler[6] has shown that the first step involves formation of a cyclic peroxide from the enol which may be cleaved either by heating or by treating with alkali to a carbonyl compound and an organic acid. In our example of the air oxidation the resonating anion (I) derived from quininone is converted to a peroxide (II) which undergoes cleavage to quininic acid (III) and 2-keto-5-vinylquinuclidine (IV), an unknown type of bicyclic amide with the nitrogen atom at a bridgehead.[12]

Having failed in several attempts to isolate the intermediate (IV) and thus observe its properties, we suggest that the isolation of meroquinene *t*-butyl ester under the mild conditions described, indicates that the bicyclic amide (IV) reacts rapidly with *t*-butyl alcohol or its anion. The inordinate reactivity thus ascribed to IV is completely uncharacteristic of amides, which are distinguished by stability to alcohols under neutral or basic conditions, but is not surprising in view of the special circumstances in the position of the amide link in IV.

Experimental

Autoxidation of Quininone.—A solution of 2.6 g. (0.067 mole) of potassium in 200 cc. of absolute *t*-butyl alcohol was shaken with oxygen at 32 lb. in a Parr hydrogenation apparatus overnight. Although no measurable amount of oxygen was absorbed, the solution became slightly yellow. There was now added an absolute tertiary butyl alcoholic solution of 10.69 g. (0.033 mole) of quininone. The resulting reddish orange solution (color is due to the salt of quininone) was shaken with oxygen at 32 lb. Within five minutes, 2.8 lb. of oxygen was absorbed (theoretically required for one mole equivalent is 2.7 lb.) the reddish-orange color being displaced by yellow, and the temperature in the reaction flask rising to 52°. No additional oxygen was absorbed on shaking fifteen minutes longer.

The cooled solution was neutralized with 1.9 cc. (0.033 mole) of acetic acid and distilled almost to dryness *in vacuo*. An oil separated from the residue on dilution with 100 cc. of ice-water and was extracted thoroughly with ether (ten 50-cc. portions). The ethereal solution was washed with saturated sodium chloride, dried overnight with sodium sulfate, and evaporated to dryness. Evaporative distillation of the residual red oil (5.3 g.) at 127° and 20 mm. gave 4.3 g. (58%) of the colorless liquid meroquinene *t*-butyl ester (V), showing, after repeated distillation, a bluish purple fluorescence in sunlight, $n^{30}D$ 1.4660, d^{30}_4 0.9832, $[\alpha]^{29}D$ +50.0° (*c* = 0.43 g./cc. in ethanol).

Anal. Calcd. for $C_{13}H_{23}O_2N$: C, 69.30; H, 10.29; N, 6.22. Found: C, 68.91; H, 10.02; N, 6.16. Neut. equiv.: Calcd.: 225. Found: 222 (brom phenol blue).

When the aqueous layer from the above ether extraction was adjusted to *p*H 5-6 with hydrochloric acid, 5.7 g. of quininic acid precipitated. From the concentrated mother liquor an additional 0.2 g. precipitated. The total yield of crude quininic acid (III) was 5.9 g. (92%). Crystallization from a large volume of ethyl alcohol gave quininic acid which darkened at 255°, finally decomposed at 278°. The melting point behavior was identical with that of an authentic sample of quininic acid. Our sample and the authentic both exhibited blue fluorescence in alcohol solution.

Quininic acid was further identified by conversion to the methyl ester by treating with methyl alcoholic hydrogen chloride at room temperature for four days. Methyl quininate was obtained as colorless needles, m. p. 85–86°. Mixed with an authentic sample of methyl quininate, m. p. 85–86°, no depression was shown.

Attempts to oxidize a solution of the potassium salt of quininone in benzene in the absence of potassium *t*-butoxide failed to give identifiable products. Oxygen was absorbed but neither quininic acid nor a derivative of meroquinene could be isolated. The uptake of oxygen was much slower.

Quininone (0.33 mole) was shaken for one week with oxygen at 30 lb. in the Parr hydrogenation apparatus in 250 cc. of *t*-butyl alcohol containing no potassium *t*-butylate. No definitely measurable amount of oxygen was absorbed. The residue obtained by boiling off solvent *in vacuo* was dissolved in 400 cc. of ether. From the ether solution there was removed a small amount of intractable material not identical with quininic acid. A 10% sodium hydroxide extract of the ether solution yielded no quininic acid on neutralization. Treatment of the ethereal solution gave 9.0 g. of solid material from which 7.0 g. of pure quininone (m. p. and mixed m. p.) was obtained by crystallization from alcohol-ether.

Quininic Acid from Quinine (Experiment by L. K. Knox).—To a solution of 5.16 g. (0.0462 mole) of potassium in 90 cc. of anhydrous *t*-butyl alcohol there was added 5.0 g. (0.0154 mole) of quinine. The clear pale yellow solution was brought to boiling and a slow stream of dry air passed into it for eleven hours. The cool mixture was diluted with an equal volume of ether and extracted with three 20-cc. portions of 20% aqueous sulfuric acid. The combined acid layers were washed with three small portions of ether and made alkaline with 20% aqueous sodium hydroxide. The liberated alkaloid was extracted with three 25-cc. portions of ether. The combined ether layers were washed with two 15-cc. portions of cold, saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated to yield 2.14 g. (42.8%) of alkaloid.

Treatment of the recovered alkaloid in 3 cc. of hot 95% ethanol with a hot solution of 0.50 g. of *d*-tartaric acid in 3 cc. of 95% ethanol gave, on standing several hours in the cold, 2.48 g. of quinine neutral tartrate, m. p. 200–205° (dec.), representing 38.6% of the quinine used originally.

The dark red alkaline layer remaining after extraction of the free bases on acidification with 20% aqueous sulfuric acid and scratching, gave, on standing several hours, 0.85 g. of quininic acid (27.2% of the theoretical). On recrystallization from absolute ethanol it melted at 278° and did not depress the melting point of an authentic sample. On the basis of quinine consumed, the yield was 44.0%.

Characterization of Meroquinene *t*-Butyl Ester (V). (a) **Reaction with Nitrous Acid.**—The previously described liquid (V) reacted with nitrous acid in dilute hydro-

(9) Conant, Kamerling and Steele, THIS JOURNAL, **53**, 1615 (1931); Steele, *ibid.*, **53**, 3171 (1931).

(10) Kohler and Barnes, *ibid.*, **56**, 211 (1934).

(11) James and Weissberger, *ibid.*, **59**, 2040 (1937).

(12) Dr. Woodward has informed us that work has been in progress in his Laboratory since 1941 on the preparation of amides of this type and has called our attention to the unusual features of the incorporation of the amide link in this environment: "In IV the atoms attached to the carbon of the carbonyl group and to the nitrogen atom at a bridgehead cannot attain coplanarity. Consequently normal amide resonance, which involves some double bond character for the C-N link, will be inhibited. Accordingly amides of this type would be expected to exhibit the reactive properties of a more or less isolated carbonyl group."

chloric acid to give a precipitate which was insoluble in acid and extractable with ether.

(b) **Hydrolysis.**—A solution of 1.00 g. of V was boiled under reflux for two hours with 15 cc. of 15% hydrochloric acid. The solution was evaporated to dryness *in vacuo*. A solution of the remaining oil in 10 cc. of water was treated with an excess of silver oxide, filtered, freed of silver ion by precipitation with hydrogen sulfide, and finally evaporated to dryness. Trituration of the residue in ethyl alcohol induced the formation of crystals which could be recrystallized from ethanol–methanol, ethanol–water, or methanol–ethyl acetate mixtures. In this way 0.75 g. (84%) of meroquinene was obtained, m. p. 220–221° (with decomposition even on rapid heating). When heated slowly meroquinene started to decompose at 194°; $[\alpha]^{26}D$ +28.6° (c = 0.081 g./cc. in water).

Anal. Calcd. for $C_9H_{15}O_2N$: C, 63.87; H, 8.94; N, 8.28. Found: C, 63.67; H, 9.36; N, 7.89.

Koenigs[13] reported for meroquinene, m. p. 220–222°, and $[\alpha]D$ +27.5°.

(c) **N-Acetylmeroquinene.**—A solution of 0.6 g. of the meroquinene obtained as above in 6 cc. of acetic anhydride was boiled for three hours under reflux. The residue obtained on evaporation of the solvent solidified on trituration with ethyl alcohol–ether. Recrystallization to give pure N-acetylmeroquinene was best effected by boiling the crude material in a small amount of water for a few minutes and allowing the resulting solution to remain in the ice-box. The pure material sintered at 107° and melted at 110°. Koenigs[13] reported N-acetylmeroquinene, m. p. 110°, and Dirscherl and Thron[14] reported m. p. 110–111°.

(d) **Transesterification.**—An absolute ethanolic solution of 0.17 g. of meroquinene *t*-butyl ester containing a trace of sodium ethoxide was allowed to stand for a week. Hydrogen chloride was passed in until the solution was acidic. A small amount of salt was removed and the solution was evaporated to dryness. Recrystallization of the residue from absolute ethanol gave 0.10 g. of meroquinene ethyl ester hydrochloride, m. p. 165°. Koenigs[13] and Dirscherl and Thron[14] reported m. p. 165 and 168°, respectively.

(13) Koenigs, *Ann.*, **347**, 143 (1906).

(14) Dirscherl and Thron, *ibid.*, **521**, 48 (1936).

Summary

The autoxidation of quininone, occurring with great ease in the presence of tertiary butoxide ion, gives rise to quininic acid and meroquinene *t*-butyl ester. The possible relation of the formation of the latter to the theoretical problem of bicyclic amides with a bridgehead nitrogen atom is discussed.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of 1,2,4-Triazole and of Pyrazole

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In view of the well-known uses of heterocyclic compounds in chemotherapy it was of interest to synthesize a number of 1,2,4-triazole derivatives for pharmacological studies. During the investigation an arsenic-containing intermediate gave rise to a 4-hydroxypyrazole type and several such derivatives were accordingly prepared.

Ethyl α-acetoglyoxylate-*p*-nitrophenylhydrazone (I) was synthesized by a method based on that of Bowack and Lapworth[2] and brominated according to a modification of the procedure of Chattaway and Ashworth[3] to give ethyl α-bromoglyoxylate-*p*-nitrophenylhydrazone (II). Treatment of II with potassium cyanate in the aqueous alcohol solvent as used by Fusco and Musante[4] in the synthesis of the triazole (IV) was unsatisfactory. Employing anhydrous methanol as a solvent gave better yields of the triazole but an ester interchange produced V, the corresponding methyl ester of IV. The poor quality and yields of the triazole derivative were attributed to a number of undesirable side-reactions between the basic decomposition products of the unstable potassium cyanate and the alkali-sensitive bromo compound II.

A different method of synthesis of IV was therefore devised. A mixture of II and excess ammonia in absolute alcohol was stirred for a minimum length of time and good yields of ethyl α-aminoglyoxylate-*p*-nitrophenylhydrazone (III) were obtained. Treatment of this compound with phosgene produced 1-(*p*-nitrophenyl)-3-carbethoxy-5-hydroxy-1,2,4-triazole (IV), the melting point 243–244° contrasting with the 235° reported by Fusco and Musante[4] for IV. Repeated recrystallizations of the compound obtained by their method yielded a substance identical with that prepared in this laboratory by the new method.

Reduction of IV with hydrogen and Raney nickel[5,6] resulted in good yields of VI which was readily arsonated by the Bart reaction[7] giving the arsonic acid (VII).

Saponification of IV produced the free carboxylic acid (VIII) but attempts to decarboxylate this acid gave indefinite results. Hydrazine in alcohol converted IV to the acid hydrazide (IX) and nitrous acid acted upon IX to yield the acid azide (X). Attempts to produce the corresponding amine from X by the Curtius degradation reaction were unsuccessful.

A mixture of phosphorus pentachloride and phosphorus oxychloride, followed by alcohol digestion, converted IV to the 5-chloro compound (XI) and XI reacted with morpholine to give the

(1) Parke, Davis and Company Fellow.

(2) Bowack and Lapworth, *J. Chem. Soc.*, **87**, 1854 (1905).

(3) Chattaway and Ashworth, *ibid.*, 475 (1933).

(4) Fusco and Musante, *Gass. chim. ital.*, **68**, 665 (1938).

(5) Mozingo, "Organic Syntheses," **21**, 15 (1941).

(6) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

(7) Bart, *Ann.*, **429**, 55 (1922).