[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Utilization of Isoamyl α-Methoxyethyl Ketone in the Pfitzinger Synthesis[1]

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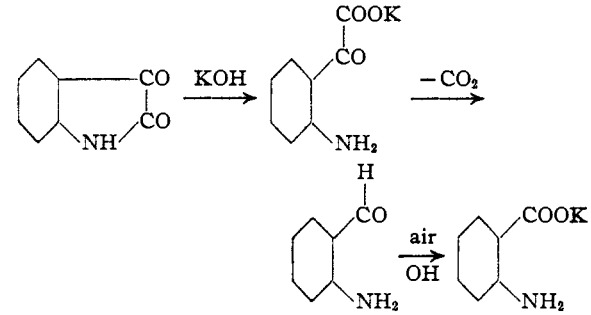
Although the utilization of simple aldehydes and ketones in the Pfitzinger reaction[3] has been studied frequently, employment of bifunctional carbonyl compounds in this synthesis has received but little attention. The first use of keto ethers of the type R—O—CH_2COCH_2R' involved aryloxy ketones[4] and soon thereafter utilization of alkoxy ketones[5] also was successful in producing cinchoninic acids containing an R–O– substituent in the 3-position. More recently we[6] investigated the behavior of keto ethers having a more branched structure, namely, R—O—$CH(CH_3)COR'$. The cinchoninic acids thus produced from 1-alkoxyethyl methyl ketones possess a 1-alkoxyethyl substituent attached to the 2-position and are more resistant to decarboxylation than are their 3-R–O– isomers. And the cleavage of their ether linkage, with subsequent reduction of the alcohol to the 2-alkyl group, during decarboxylation was unexpected.[6] Therefore, it was decided to extend the study to certain higher homologs in the alkyl 1-alkoxyethyl ketone series.

In this investigation attempts were made to convert isoamyl 1-methoxyethyl ketone[7] into 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid under the usual conditions of the Pfitzinger synthesis, namely, through interaction with isatin in the presence of 33% potassium hydroxide solution. However, when so heated at 100° for twenty-four hours with the aqueous solution, or in diluted alcohol solution, most of the ketone did not enter into reaction, and evolution of ammonia was noted; from the reaction mixture only cinchoninic acid was isolated. When 40% potassium hydroxide (aqueous) solution was used, reaction occurred and a product, $C_{24}H_{28}N_2O_5$, resulted. This product was shown to yield equimolecular amounts of the desired substituted cinchoninic acid and anthranilic acid. The formation of the anthranilic acid was established as resulting from interaction of isatin and the concentrated alkali.[8]

The molecular compound is quite stable; it is separated into its two components with difficulty and, upon diazotization, the amino group of anthranilic acid in the compound is replaced by



hydroxyl, without any other alteration or cleavage of the molecular compound. Since this stable compound results also from interaction of the 2,3-disubstituted cinchoninic acid and salicylic acid, it is believed that the initial molecular combination results from reaction of the carboxyl group of anthranilic acid and the tertiary amino group of the quinoline acid.[9] Microsublimation permits separation of the salt into its two components.

Straightforward decarboxylation of 3-isobutyl-2-(1-methoxyethyl)-cinchoninic and was unsuccessful, but hydrolysis and reduction yielded the anticipated products.

Experimental

Interaction of Isoamyl 1-Methoxyethyl Ketone with Isatin.—As the first attempt to prepare 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid, 22.5 g. (0.15 mole) of isatin was dissolved in 110 g. of warm 33% aqueous potassium hydroxide solution, 21.5 g. (0.16 mole) of isoamyl 1-methoxyethyl ketone[7] was added and the mixture was heated at 100° for twenty-four hours; the ketone layer showed little or no decrease in volume. The upper layer was separated and yielded 18.9 g. of unreacted ketone (88% recovery). Acidification of the water layer did not produce any quinoline acid.

In another trial, the same amounts of reactants were used, but enough alcohol was added to form a homogeneous solution. Again, the mixture was heated under reflux on a steam-bath for twenty-four hours; the evolution of a small amount of ammonia was noted during the first portion (three to four hours) of the period of heating. From the reaction mixture 10.5 g. (about 50%) of unaltered ketone was regained; acidification of the residual reaction mixture yielded resinous material from which no crystalline solid was obtainable.

When a 33% solution of potassium hydroxide was prepared using 1:3 water–alcohol as a solvent, and this reaction mixture was heated, as before ammonia was evolved. The solution was chilled overnight and the solid which separated was recrystallized from glacial acetic acid; m. p. 256.0–257.5° (cor.) (dec.). The melting point behavior was unchanged after two recrystallizations from hot water. When mixed with an authentic sample of cin-

(1) From the M.A. Thesis of A. F. Isbell, August, 1941.

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(3) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); *ibid.*, **38**, 582 (1888); *ibid.*, **56**, 283 (1897).

(4) Calaway with Henze, THIS JOURNAL, **61**, 1355 (1939).

(5) Cross with Henze, *ibid.*, **61**, 2730 (1939).

(6) Lesesne with Henze, *ibid.*, **64**, 1897 (1942).

(7) Wallace and Henze, *ibid.*, **64**, 2882 (1942).

(8) A somewhat similar behavior is the conversion of isatin into aniline by heating in a retort with potassium hydroxide [Hoffmann, *Ann.*, **53**, 11 (1845)].

(9) Davis [U. S. Patent 1,203,499; through *C. A.*, 11, 185 (1917); British Patent, 102,136; through *C. A.*, 11, 524 (1917)] has claimed the formation of a molecular compound between 2-phenylcinchoninic acid and salicylic acid as a result of dissolving equimolecular amounts of their alkali salts in water and acidifying the mixture with hydrochloric acid.

choninic acid [m. p. 257.5° (cor.) (dec.)],[10] the melting point was unaltered.

Finally, 9.28 g. (0.0631 mole) of isatin was dissolved in 80 cc. of 40% aqueous solution of potassium hydroxide; some crystals of potassium isatinate separated. There was added 10 g. (0.0631 mole) of isoamyl 1-methoxyethyl ketone and the well-stirred mixture was heated under reflux at 100° for twenty-four hours. Since the mixture was not homogeneous, it was heated to boiling for twelve hours; the layer of ketone markedly decreased in volume. After chilling overnight a gummy solid had separated. The solid was filtered off, dissolved in warm water, and the solution was extracted with ether to recover 3.5 g. of the unreacted ketone. The alkaline solution was acidified cautiously with hydrochloric acid to the point of maximum precipitation of a tan-colored, amphoteric solid. The latter was removed by filtration, dissolved in dilute potassium hydroxide solution, treated with norite, reprecipitated by acidification, and dried; m. p. 216.5–217° (cor.) (dec.); weight 11.25 g. After two recrystallizations from 15% ethyl alcohol, the material was in the form of a pale, straw-colored, amorphous powder melting with decomposition at 221.5–222.0° (cor.). It is only slightly soluble in boiling water, but once dissolved it separates with difficulty from cold water. It is very soluble in ethyl alcohol, less soluble in acetone and ethyl acetate and practically insoluble in benzene, ether and carbon tetrachloride. That the product was not the anticipated disubstituted cinchoninic acid ($C_{17}H_{21}NO_3$) was indicated by the following data:

Anal. Calcd. for $C_{17}H_{21}NO_3$: mol. wt., 287.35; C, 71.22; H, 7.37; N, 4.88. Found: mol. wt. (Rast), 210.3, (boiling point elevation) 205.6; neut. equiv. (assuming one —COOH), 216.8; C, 67.87; H, 6.67; N, 6.85. Calcd. for $C_{24}H_{28}N_2O_5$: mol. wt., 424.48; C, 67.90; H, 6.65; N, 6.60.

When dissolved in hot ethyl acetate, upon cooling very slowly, long, perfectly white crystals separated in rosettes. The first crop of crystals (A) melted with slight decomposition at 194–196° (cor.), a second crop at 220–220° (dec.) and the last (C) at 155–160° (dec.). The last material (C) was recrystallized twice from water to melt with decomposition at 144–145° (cor.); mixed with an authentic sample of **anthranilic acid** (m. p. 144–145°) the m. p. was unchanged.

Anal. Calcd. for $C_7H_7NO_2$: C, 61.37; H, 5.23. Found: C, 61.43; H, 5.15.

The identity of this material was further established by preparation of its acetyl derivative [m. p. 185° (cor.)] and by conversion, through diazotization, into salicylic acid.

The purified material (A) melting at 195–196° (cor.) is only slightly soluble in water, soluble in acetone, ethyl alcohol and dioxane, insoluble in benzene, ether, and carbon tetrachloride.

Anal. Calcd. for $C_{17}H_{21}NO_3$: neut. equiv., 287.35; C, 71.22; H, 7.37; N, 4.88. Found: neut. equiv., 283.6; C, 71.15; H, 7.36; N, 5.01.

It was also found that the material melting at 222° could be separated into two portions by fractional sublimation under 5–10 mm. pressure. The first fraction sublimed at 140–150° and on purification melted with decomposition at 144–145° (cor.). The material subliming at 185–195°, after one crystallization from ethyl acetate melted with slight decomposition at 195–196° (cor.).

These data indicate that the product formed by interaction of potassium isatinate and isoamyl 1-methoxyethyl ketone is a salt (or molecular compound) derived from anthranilic acid (C) and 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid (A). Hence, approximately equimolecular amounts of these two acids were dissolved in a small amount of hot water; on chilling, pale yellow crystals separated which melted with decomposition at 220° (cor.). Moreover, a dry mixture of equal quantities of the two component acids melted with decomposition at 220–222°.

(10) Skraup [*Ann.*, **201**, 301 (1880)] reported m. p. 253–254° (uncor.).

Five grams of the salt (m. p. 222°) was diazotized at 0°, and then the solution was heated to boiling until evolution of nitrogen ceased. At the boiling point the solution developed a deep red color and crystals began to separate. Upon cooling and filtering, 3.6 g. of crystals was obtained. By recrystallization from diluted dioxane there was obtained white crystals melting with decomposition at 220.5° (cor.). An aqueous solution of this material gave a violet color with dilute ferric chloride solution; the neut. equiv. was 216. The material was fractionally sublimed at 10 mm. pressure; at 100–120°, white crystals were obtained and, after recrystallization from water, melted alone, or mixed with an authentic sample of **salicylic acid**, at 157.5–158.5°. The residue left in the sublimation flask was recrystallized from ethyl acetate to melt at 195-196° (dec.).

These data indicate that the product obtained by diazotization is a molecular compound derived from salicylic acid and 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid. Therefore, equimolecular quantities of these two acids were dissolved in hot water and heated for two hours. On chilling, white crystals melting with decomposition at 218.5–219.0° were obtained. Recrystallization from diluted dioxane caused the m. p. to become 219.0–220.5° (cor.) (dec.). The m. p. was unaltered by mixture with the product obtained through diazotization.

Preparation of 3-Isobutyl-2-(methoxyethyl)-cinchoninic Acid.—Forty grams (0.253 mole) of isoamyl 1-methoxyethyl ketone[7] and 50 g. (0.34 mole) of isatin were added to 305 cc. of 40% potassium hydroxide solution and heated under reflux with stirring at 115–120° for twenty-four hours; practically all of the ketone layer had disappeared. The mixture was chilled and gummy, semi-solid material was filtered off, dissolved in a small amount of warm water, and the solution was extracted three times with ether to recover 3.5 g. of ketone. After filtration the extracted solution was acidified with hydrochloric acid as long as precipitation resulted. The solid was treated with sodium bicarbonate solution in order to separate a small amount of undissolved isatin. The solution was again neutralized and filtered; yield, 68.4 g. of pale yellow solid. The latter was dissolved in ethyl acetate, concentrated somewhat and slowly cooled. Initially, white needles crystallized; when yellow rosettes also began to form, the white needles were removed by filtration and dried. Thus was obtained 31 g. (46% yield based on 36.4 g. of ketone) of the substituted cinchoninic acid melting with slight decomposition at 195–196° (cor.). On further concentration of the filtrate and chilling, 39.4 g. of the molecular compound (with anthranilic acid) was obtained.[11]

Attempted Decarboxylation of 3-Isobutyl-2-(1-methoxyethyl)-cinchoninic Acid.—Five grams of this acid in a distilling flask was heated in an oil-bath at 220–230° (25–35° above the m. p. of the acid) until the crystals fused and ceased to evolve gas. The pressure in the flask was reduced to 5 mm. and the bath temperature was raised to 285°; the residue in the flask became more viscous and increasingly dark in color, but no distillate was noted. The residual material could not be crystallized, did not dissolve in water saturated with sulfur dioxide, nor yield a picrate from alcoholic solution.

Another 5-g. portion of the acid was dissolved in 3.5 cc. of 20% potassium hydroxide solution, 0.5 g. of calcium oxide was added and the water removed from the mixture by heating in a bath at 150–160°. Upon adequate elevation of the bath temperature, decomposition occurred with evolution of gas, but the residue did not yield a quinoline derivative or form a picrate.

Action of Hydrochloric Acid on 3-Isobutyl-2-(1-methoxyethyl)-cinchoninic Acid.—Three grams of the substituted quinoline and 5 cc. of concentrated hydrochloric acid were sealed in a Carius tube and heated at 160–170° for two hours. The content of the tube was evaporated to dryness, redissolved in a small amount of water and an

(11) This molecular complex contains 67.7%, or in this instance 26.7 g., of the 2,3-disubstituted cinchoninic acid. Hence, the total conversion of ketone to quinoline derivative was essentially quantitative.

excess of ammonium hydroxide solution was added. The excess was removed by boiling and a slight excess of acetic acid was added. On chilling the solution, a white solid separated in the form of small cubes; after drying, the material weighed 2.39 g. (84% yield). Upon purification by solution and reprecipitation, the **2-(1-hydroxyethyl)-3-isobutylcinchoninic acid** melted at 213.5–214.0° (cor.) (dec.).

Anal. Calcd. for $C_{16}H_{19}NO_3$: neut. equiv., 273.32; C, 70.31; H, 7.01; N, 5.13. Found: neut. equiv., 270.6; C, 70.00; H, 7.00; N, 5.11.

Action of Hydriodic Acid on 3-Isobutyl-2-(1-methoxyethyl)cinchoninic Acid.—As a result of heating 3 g. of this acid with 5 cc. of 57% hydriodic acid in a sealed tube at 160–170° for two hours, a 72% yield of the same hydroxyethyl derivative was obtained.

However, when 2.5 g. of the methoxyethyl derivative and 10 cc. of 57% hydriodic acid were heated in a sealed tube at 160–170° for forty-eight hours, reduction as well as hydrolysis occurred and there resulted 1.55 g. (87% yield) of **2-ethyl-3-isobutylcinchoninic acid**, which melted with decomposition at 206–207° (cor.).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 74.67; H, 7.45; N, 5.44. Found: C, 74.51; H, 7.55; N, 5.40.

By heating together 2.06 g. of 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid, 1 g. of red phosphorus and 10 cc. of 57% hydriodic acid in a sealed tube at 160–170° for forty-eight hours, a further degree of reduction occurred and 1.74 g. (93% yield) of **2-ethyl-3-isobutyl-1,2,3,4-tetrahydrocinchoninic acid** was produced. The latter melts with slight decomposition at 212.5–213.0°; when mixed with 2-(1-hydroxyethyl)-3-isobutylcinchoninic acid, the mixture melted at 184–202°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.78; N, 5.36. Found: C, 73.61; H, 8.81; N, 5.30.

Conversion of Isatin into Anthranilic Acid.—In order to establish the origin of the anthranilic acid isolated in the interaction of potassium isatinate and isoamyl 1-methoxyethyl ketone (page 2097), 10 g. of isatin was dissolved in 62 cc. of 40% potassium hydroxide solution and the solution was boiled under reflux for eight hours. During this period evolution of a small amount of ammonia was noted. The alkaline solution was chilled overnight, causing separation of crystalline material. The latter was dissolved in warm water, the solution was filtered and made barely acidic with hydrochloric acid. White crystals separated, were removed by filtration, and dried; weight 8.5 g. (91% yield) when recrystallized from hot water to melt with decomposition at 145° (corr.).[12] A mixture with an authentic sample of anthranilic acid melted at the same temperature.

Summary

1. In the attempted preparation of 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid, from interaction of isoamyl methoxyethyl ketone and isatin through the Pfitzinger synthesis, a molecular compound between that acid and anthranilic acid was obtained.

2. Separation of this molecular compound into its two components was accomplished through fractional sublimation.

3. Diazotization of the molecular compound yielded an analogous combination of salicylic acid and 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid.

4. Whereas hydrolysis and reduction of 3-isobutyl-2-(1-methoxyethyl)-cinchoninic acid proceeded in a normal manner, decarboxylation was not straightforward.

5. Anthranilic acid was prepared in good yield by heating isatin in boiling 40% potassium hydroxide solution.

(12) Lundén [*Z. physik. Chem.*, **54**, 537 (1906)] reported m. p. of 144.3° for anthranilic acid.

AUSTIN, TEXAS RECEIVED JUNE 29, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY]

17-Isopregnan-3(α)-ol-20-one

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It has been shown by several workers[1] that steroids with a ketone group at C_{20} are partially isomerized at C_{17} by treatment with alkali. In the present work 17-isopregnan-3(α)-ol-20-one[2] was isolated from the mother liquors from the crystallization of pregnan-3(α)-ol-20-one which had been obtained by the saponification of its acetate by alkali. The acetate of pregnan-3(α)-ol-20-one was obtained by the Barbier–Wieland degradation of lithocholic acid[3] and was saponified by boiling with methanolic sodium hydroxide. After removing the alkali most of the pregnan-3(α)-ol-20-one was obtained by crystallization from cyclohexane. The filtrate was distilled to dryness *in vacuo* leaving an amorphous gum which could not be crystallized. The hydroxyl containing fraction was separated by treating the residue with succinic anhydride in pyridine and separating the acid succinate by its solubility in cold dilute alkali. By saponification of the crude acid succinate an amorphous material was obtained from which a ketone fraction was obtained by treatment with Girard reagent.[4] After decomposing the Girard reagent complex and extracting the "olone" fraction by ether, the ether solution was concentrated, giving a crystalline product. This crystalline material proved to be a mixture which

(1) (a) Butenandt and Mamoli, *Ber.*, **68B**, 1847 (1935); (b) Butenandt and Fleischer, *ibid.*, **70B**, 96 (1937); (c) Butenandt, Schmidt-Thomé and Paul, *ibid.*, **72B**, 1112 (1939); (d) Marker, Wittle and Plambeck, THIS JOURNAL, **61**, 1333 (1939).

(2) This compound has been reported by G. Müller, Danzig, Diss., 1938. "Über isomere Pregnan-ol-one (3, 20)" and abstracted by H. Seyle (Enclopedia of Endocrinology, Section 1. The Steroids, Vol. *IV*, p. 579, A. W. T. Franks Publishing Company, Canada) with the remark that the structure is uncertain. The present work indicates conclusively that the compound reported by Müller is not 17-isopregnan-3(α)-ol-20-one.

(3) Hoehn and Mason, THIS JOURNAL, **62**, 569 (1940).

(4) This reagent (acethydrazidepyridinium bromide) was prepared by a procedure similar to that used by Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936), for the corresponding chloride except that ethyl bromoacetate was used in place of ethyl chloroacetate. It is a stable crystalline compound.