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SYNTHESIS OF ETHYL QUININATE[1]

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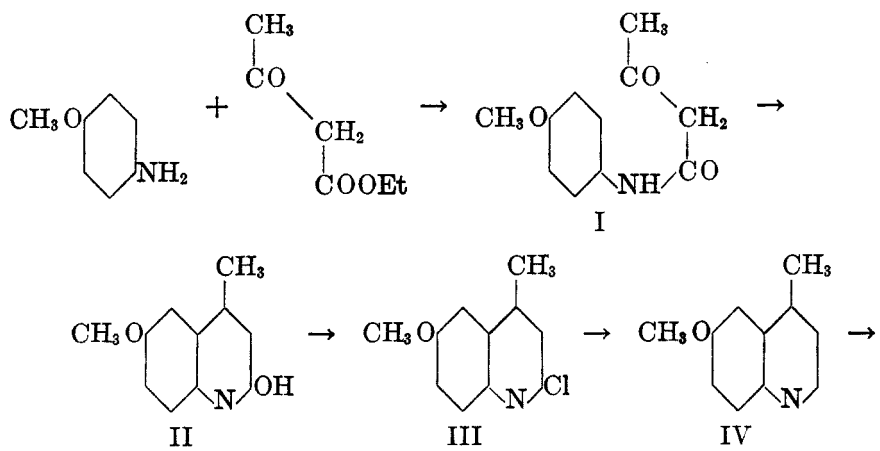
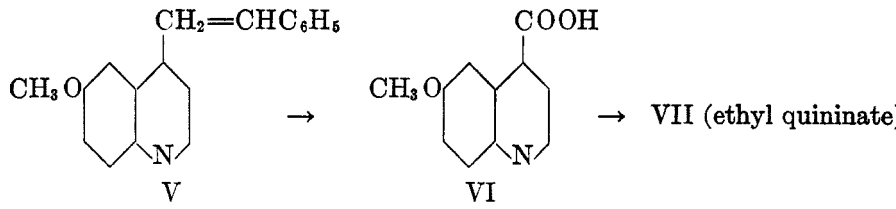
Early in 1942, when the advent of war had made an intensive search for new antimalarials imperative, one of the most promising fields of study appeared to be that of the 6-methoxy-4-quinolyl carbinols. For this work we needed relatively large amounts of quininic acid, which of course could no longer be made by the usual procedure of oxidation of quinine.

There were recorded in the literature, however, four different syntheses of quininic acid, each starting from *p*-anisidine, and it was hoped that at least one of these might prove adaptable to large-scale work. Inasmuch as it involved an expensive iodine oxidation, and the over-all yield was found by Ainley and King (1) to be very low, the synthesis developed by Kaufmann (2) was not deemed suitable. It was considered that the syntheses of Halberkann (3) and Thielepape (4) held some promise. The latter two have been investigated in detail by Buchman, who will publish his results elsewhere.

The fourth method, developed by Rabe *et al.* (5) and improved upon by Ainley and King (1), was thought likely to be the most promising for large-scale work. Special attention has therefore been devoted to the problem of increasing the yields in the seven steps involved in this synthesis, which are as follows:



[1]The work reported here was done in part under contracts recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Notre Dame and Columbia University.



This synthesis was reinvestigated on a laboratory scale by a group at the University of Notre Dame,[2] and the procedures they developed were further modified and then adapted to pilot-plant scale by workers at Columbia University and the Research Laboratories of Merck and Company.[3] Simultaneously and quite independently, two of us (R. S. T. and M. A. C.) at Mellon Institute devoted some attention to improvements in the methods and later agreed to joint publication. As a result of these studies, many important details not mentioned by the earlier workers (1, 5) have been observed, the procedures have been so modified as to simplify the experimental work or improve the yields (or both), and all the operations have been performed on a much larger scale than previously. The present paper embodies the most important results obtained by the various groups mentioned above.

In the preparation of *p*-acetoacetanisidide, I, it has been found possible either to lessen the proportion of acetoacetic ester recommended by Ainley and King (1) without lowering their yield (81%), or to retain their proportions and raise the yield to 93%. If one takes into consideration the recovery of unchanged starting materials, the yield is practically quantitative. The ring-closure step (I → II) could be carried out on a much larger scale (up to 1 kg. in the laboratory) without appreciable diminution in yield (75–80%), and the isolation and purification of the product was simplified considerably.

Ainley and King (1) reported a 98.5% yield for the preparation of the 2-chloro compound (III) but none of the workers in the present group has been able to duplicate this yield. Furthermore, it has been found that the temperature (130–140°) recommended by Ainley and King is too high, the reaction being smoother at lower temperature (110–120°). In addition, better methods of isolation and purification have been developed.

The 2-chloro compound (III) can be converted to 6-methoxylepidine (IV) by reduction or by catalytic hydrogenation. Ainley and King had hydrogenated the chloro compound in glacial acetic acid-sodium acetate solution over palladized charcoal; in the present work it was discovered that the hydrogenation could be

[2]The authors acknowledge some technical assistance rendered by Dr. James F. Kerwin, Dr. Eldred E. Young, and Mr. James M. Constantin.

[3]We wish to thank Merck and Company for their generosity in placing their facilities at our disposal without charge.

[4]After the present work had been completed, Campbell and Schaffner (6) described a modified Doebner-Miller synthesis whereby 6-methoxylepidine could be obtained from *p*-anisidine in 52% yield in one step. If large amounts of this lepidine derivative should be needed in the future, this one-step preparation may supplant the four-step synthesis described here.

carried out equally well in warm alcoholic potassium hydroxide in the presence of Raney nickel, and that the lepidine was then more easily isolated. However, it was also found that the reduction of III to IV could be brought about by zinc and acetic acid, a much simpler procedure. The yield by both methods was almost quantitative[4] (95–98%).

6-Methoxy-4-styrylquinoline (V) was prepared essentially according to Rabe (5), except that the water formed in the reaction was continuously removed by distillation, and a procedure was developed for avoiding isolation of the styrylquinoline acid sulfate. It was found that the crude styryl compound could be used direct'y for oxidation, thus avoiding the tedious recrystallization from ligroin. Since Bulach (7) had found that acetic anhydride facilitates condensation between quinaldine and *p*-nitrobenzaldehyde to yield the corresponding styryl derivative, it was of interest to learn whether it is as efficient as zinc chloride in the present condensation. It was found that it gives a yield (41%) inferior to that obtained with zinc chloride.

The styryl compound was oxidized to quininic acid in 50% pyridine, as described by Ainley and King (1), and in acetone. The yield was about the same in either solvent, but the use of acetone greatly facilitated isolation of the product. Quininic acid was then esterified with ethanol in the presence of sulfuric acid; it was found easier to purify the ester (VII) by crystallization than by distillation.

In Table I the results of the present work are compared with those of the earlier workers, from which it may be seen that the highest laboratory yields we have obtained considerably exceed those of Ainley and King, our over-all yield being some 63% greater. Routine laboratory preparations and pilot plant preparations gave somewhat lower yields, but it is expected that further refinements in the industrial technique for step VI → VII will make ethyl quininate available at a not-too-exorbitant cost.

Since Rabe did not give the yield of I, but intimated that it was the same as that of Limpach (8) (90%), and for V gave only the yield of crude sulfate, the over-all yield we have calculated for his work is a liberal approximation.

EXPERIMENTAL

p-Acetoacetanisidide (I), SN 6788,[5] *Procedure A* (Mellon). Ethyl acetoacetate (1015 ml., 8 moles *reagent* grade) was placed in a 3-necked, 2-liter flask provided with thermometer and mechanical stirrer, and having one neck open. The ester was heated to 160–165° (bath temp., 175–176°) and *p*-anisidine (246 g., 2 moles) added in portions with stirring during 45 minutes; the mixture was kept at this temperature a further 30 minutes, allowed to cool, kept overnight in the refrigerator, and filtered. The air-dried crystals (426 g.) were stirred with pentane (500 ml.) to remove adhering ethyl acetoacetate, filtered, washed with pentane (50 ml.), air-dried, and then dried at 60°; weight, 370 g. (Unchanged ester was recovered by evaporating the pentane filtrate plus washings to dryness.)

The mother liquor of the first crop was evaporated to dryness under reduced pressure (bath at 110°), and the crystalline residue freed from *p*-anisidine as follows: It was dissolved

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[5]The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these drugs will be tabulated in a forthcoming monograph.

in chloroform (430 ml.) and 430 ml. of hexane was added, the solution nucleated, and kept overnight in the refrigerator. The second crop weighed 16 g., making the total yield of I, 386 g. (93%); m.p. 116–117°. Limpach (8) reported a yield of 90%. This material is pure enough for the next step.

For analysis, it was recrystallized by dissolving 20 g. in 100 ml. of chloroform, filtering, adding 100 ml. of hexane in portions, and cooling the mixture for several hours. The colorless crystals so obtained (14.8 g.) melted at 118–119°, in agreement with the value given by Ainley and King (1). Others have reported the melting point as 115–116° (9).

Anal.[6] Calc'd for $C_{11}H_{13}NO_4$: C, 63.73; H, 6.3; N, 6.76.
Found: C, 63.85; H, 6.3; N, 7.24.

Procedure B (Notre Dame). Yields of 80–85% may be obtained when a smaller excess of acetoacetic ester is used; it was found convenient to add *p*-anisidine in the molten state. In a typical experiment, 500 ml. of acetoacetic ester (*practical* grade) was heated to 165°, 200 g. of molten *p*-anisidine (*practical*) was added from an electrically-heated dropping-funnel, with mechanical stirring, during 45 minutes and then treated as in procedure A, giving 236 g. of cream-colored crystals, m.p. 118–119°. A second crop was obtained by concentration of the mother liquor, making the total yield 80–85%.

2-Hydroxy-6-methoxylepidine (II), SN 6846, Procedure A (Mellon). Concentrated sulfuric acid (*d*, 1.84; 137.5 ml.) was added, *without cooling*, to 250 g. of dry, recrystallized *p*-

TABLE I

YIELDS IN THE SYNTHESIS OF ETHYL QUININATE

WORKER	I	II	III	IV	V	VI	VII	OVER-ALL, I–VII
Rabe	90 (?)	*ca.* 100	75	90	100 (?)	—	80	*ca.* 50 (?)
Ainley & King	81	80	98.5	97.5	81	84.5	82	34.9
Present:								
Lab.—highest	93 (100)	83	94	98	94	95	90	57 (61.5)
Lab.—average	80–85	75–80	75–85	90–98	85–90	70–85	80–90	
Pilot plant	—	78	85–90	87	84	—	53	

methoxyacetoacetanilide in a two-necked flask (thermometer). The flask containing the mixture (temp. 60°) was then attached to a reflux condenser ("Drierite" tube) and placed in a glycerol bath at room temperature. The bath temperature was raised, during 105 minutes, until the reaction temperature reached 100° (bath temp. 92°). The exothermic reaction continued for 90 minutes, the reaction temperature being kept at, or slightly below, 100°; reaction product then started to crystallize. The reaction temperature was now maintained at 95° during 2 hours (bath temp. 98°), giving a yellow, almost solid mass which was cooled to 60°, removed from the flask, and kept overnight under 2.5 liters of water. It was stirred until free from lumps, filtered, washed with three 500-ml. portions of water, resuspended in water (1 liter), stirred, and kept overnight at room temperature. It was then filtered off, air-dried, dried at 60° (72 hours) and 110° (20 hours); yield 181.5 g. (79.5%); m.p. 267–268° (Al block). This material was pure enough to be used for the next step.

When 50-g. portions of anisidide were treated as above, the yield was somewhat greater (83%; m.p., 270–273°). [Rabe (5) reported an "almost quantitative" yield of impure material (m.p. 253°) having an incorrect analysis some 2% deficient in carbon; and Ainley and King (1) obtained an 80% yield of impure material (m.p. not recorded) containing "traces of unchanged" anisidide.]

[6]All analyses were performed by Dr. Carl Tiedcke, New York, N. Y. for R.S.T. and M.A.C.

It was recrystallized as follows: 10 g. was dissolved in 40 ml. of boiling glacial acetic acid (reflux), the hot solution filtered, 120 ml. of water added in portions to the filtrate, and the suspension of colorless crystals kept overnight in the refrigerator. The product was dried as above; yield 9 g.; m.p. 273–275° (Al block). Rabe (5) gave m.p. 253°; Kermack and Muir (10), m.p. 255°; Monti and Verona (11), m.p. 268°; Ainley and King (1), m.p. 268–270°; Backeberg (12), m.p. 272°.

Anal. Calc'd for $C_{11}H_{11}NO_2$: N, 7.41. Found: N, 7.50.

Procedure B (Columbia, Merck). Finely powdered I (1000 g.) was added portionwise during 45 minutes to 700 ml. of concentrated sulfuric acid in a 3-necked, 3-liter flask fitted with a thermometer and mechanical stirrer, the temperature being kept below 35°. The mixture was then warmed on a hot-water bath until the vigorous gas evolution was well under way (the temperature at which this began varied from 65° to 95°); the water-bath was replaced by an ice-bath and the temperature of the reaction mixture kept at 100° by external cooling. When the reaction had subsided the mixture was kept at 95–100° for two hours and then poured into ice-water (4 kg.). The solid was washed twice with 2-liter portions of water, suspended in 1.5 liters of ice-water, and treated with ammonium hydroxide until the mixture was basic to litmus. The yield of light gray product suitable for use in the next step was about 75%. Unless the acid was completely removed the material darkened on drying and had to be recrystallized.

2-Chloro-6-methoxylepidine (III), Procedure A (Mellon). The method of Ainley and King (1) was modified to avoid "the initial vigorous reaction," and the proportion of phosphorus oxychloride employed was diminished by one-third. It was found that the product must be entirely freed from acid, as otherwise its solubilities are considerably changed.

To 2-hydroxy-4-methyl-6-methoxyquinoline (200 g.; dried at 110°) in a 1-liter flask (ground-glass joint) was added 400 ml. of phosphorus oxychloride and the suspension heated under reflux ("Drierite" tube) in a glycerol bath, the temperature of which was raised from 25° to 90° during 30 minutes. Gentle evolution of hydrogen chloride then began and the hydroxy compound started to dissolve. During the next 20 minutes the bath temperature was raised to 108°, whereupon gentle refluxing commenced; after 10 minutes at this temperature, all the hydroxy compound had dissolved and the chloro compound started to crystallize out. The bath temperature was slowly raised to 120° during the next 30 minutes and then the mixture was allowed to cool; it was evaporated to dryness (ground-glass joints) under diminished pressure (bath temp. 60°), some 180 ml. of phosphorus oxychloride being recovered.

The solid product was now added in portions, with stirring, to a mixture of 2 liters of chopped ice with one liter of water, giving yellowish crystals which were filtered off (filtrate A), washed with three 250-ml. portions of water, stirred into a paste with 250 ml. of water, and a saturated aqueous solution of sodium biearbonate added with stirring until effervescence ceased; this neutralization of traces of acid is important. The suspension was filtered (filtrate B) and the solid washed with three 250-ml. portions of water, air-dried, and dried at 60° (48 hours); yield 197.2 g.; m.p. 145–147°. (This material is pure enough to be used in the next step.)

Filtrates A and B were united, and sodium bicarbonate was added to neutrality, giving a second crop which was washed and dried as above; wt. 4.9 g; m.p. 139–140°; total yield 202.1 g. (92%). The preparation was repeated several times, but the yield recorded by Ainley and King (1) (98.5% of material having m.p. 142–144°) could not be duplicated.

It was recrystallized as follows: 10 g. was dissolved in 68 ml. of glacial acetic acid under reflux, on a boiling-water bath. Water (34.5 ml.) was then added in 5-ml. portions through the top of the condenser, the solution cooled to room temperature, kept overnight in the refrigerator and the colorless crystals filtered off, washed with water, and dried as above and at 110° (45 minutes); yield 8.3 g.; m.p. 146–148°.

The substance (10 g.) was also recrystallized from boiling absolute ethanol (130 ml.) giving 9.2 g. of long, colorless needles having a silky sheen; m.p. 146°. Rabe (5) described the substance as "yellowish needles"; m.p. 145°.

Anal. Calc'd for $C_{11}H_{10}ClNO$: C, 63.60; H, 4.9; N, 6.75; Cl, 17.08.
Found: C, 63.24; H, 4.8; N, 6.39; Cl, 16.98.

Procedure B (Notre Dame, Columbia). It was found that the chloro compound could be isolated directly from the cold reaction mixture by filtration, while most of the tarry by-products remained in solution in the phosphorus oxychloride.

A mixture of dry 2-hydroxy-6-methoxylepidine (150 g.) and 450 ml. of phosphorus oxychloride ("purified" grade) was heated under reflux until the bath temperature reached 110°. When the inside temperature reached 100° boiling began, and the temperature rose rapidly to 105°; there was rapid refluxing and a copious evolution of gas. Occasionally it was necessary to lower the oil-bath for a few moments. After the initial vigorous reaction had subsided, the mixture was heated as in procedure A, cooled in ice, filtered through a sintered glass funnel, and the solid pressed as dry as possible. The solid was added gradually, with stirring, to a mixture of ice and water, filtered, washed thoroughly with ice-water, and finally with a small amount of boiling ethanol. The product obtained (156 g.; 94%) was a light gray, slightly impure solid, m.p. 142–145°, which could usually be dechlorinated without purification. Occasionally, however, it poisoned the catalyst, and had to be recrystallized.

Recrystallization of large amounts was difficult and troublesome, but several methods were found to be fairly satisfactory; (a) A ratio of 40 ml. of 40% sulfuric acid to 10 g. of compound, with 1 g. of decolorizing carbon, was used. The recrystallized material was washed thoroughly with water and dried; recovery of product (m.p. 142–145°) was 78%; (b) ten grams of crude chloro compound in 175 ml. of 95% alcohol was treated with 1–2 g. of Norit. The recovery, including a second crop, was 78–80% of material melting at 142–145° after sintering at 139°.

Using larger amounts of 2-hydroxy-6-methoxylepidine, the reaction gave poorer yields. Thus, when 420 g. of II and 1260 ml. of phosphorus oxychloride were caused to react as described in B, and the product isolated as described in A, the yield of crude III was 70–80%. Crystallization from 95% alcohol or 40% sulfuric acid diminished the yield of product suitable for hydrogenation to 54–62%.

6-Methoxylepidine (IV), SN 2736, Procedure A[7] (Notre Dame, Columbia). Conversion of III to IV can be effected conveniently by catalytic hydrogenolysis using Raney nickel, and the amount of chloro compound hydrogenated at one time is limited only by the capacity of the apparatus available. The reaction can be carried out at room temperature but is more rapid at 45–65°.

A mixture of 15.6 g. of III, 135 ml. of absolute alcohol, 6 g. of potassium hydroxide pellets (*reagent* grade), and 6 g. of alcohol-washed Raney nickel was shaken with hydrogen at 60 lb./sq. in. at 45–65°. Hydrogen absorption was complete in two hours. The products from several such experiments were then combined.

The clear solution obtained after removal of the catalyst (IV is much more soluble in alcohol than III) was evaporated under reduced pressure, and the resulting oil poured into water and chilled. The crystalline hydrate of IV was collected, washed with cold water, pressed, and air-dried (one to two days). The yield of material melting at 51–53° (sintering at 48°) was 94%. It was used in the next step without purification.

In a larger-scale run, 1086 g. of III was hydrogenated at room temperature and 40 lbs./sq. in. in 26 hours to give an 88% yield of IV.

Procedure B (Mellon). The following method may be used without modification for larger quantities. One hundred grams of III was dissolved in 675 ml. of glacial acetic acid plus 75 ml. of water at 70°, under reflux, with mechanical stirring. Granulated zinc (50 g., No. 30 mesh) was added in one portion, and stirring was continued during 6 hours at 70°. The hot solution was then filtered, and the unreacted zinc (11.1 g.) was washed with four 25-ml. portions of water, which were added to the main filtrate. This was evaporated to dry-

[7]Since this work was completed, a similar method has been reported by Kleiman and Weinhouse, *J. Org. Chem.*, **10**, 562 (1945).

ness under reduced pressure, and the product shaken with 1 liter of 8 *N* sodium hydroxide solution plus 600 ml. of chloroform. The aqueous layer was re-extracted with four 100-ml. portions of chloroform, the combined chloroform extracts dried with anhydrous sodium sulfate, filtered, and evaporated to dryness, giving a brown sirup (81.7 g., 98%) which crystallized on standing at room temperature. It was purified by distillation; b.p. 96–97° at 0.1 mm. (bath temp. 110–116°); colorless crystals, m.p. 31–32°. This is anhydrous 6-methoxylepidine.

6-Methoxy-4-styryl quinoline (V), SN 6845, Procedure A (Notre Dame, Columbia). One hundred grams of 6-methoxylepidine hydrate (IV), 540 g. of dry benzaldehyde (E.K. Practical, purified shortly before use by shaking with sodium carbonate solution), and 36 g. of fused zinc chloride were placed in a 2-liter flask fitted with a short still-head and condenser set for downward distillation. The flask was heated[8] in an oil-bath at 185–190° until no more water distilled over; this required about five hours. The mixture was cooled to room temperature, and the product isolated as described by Rabe (5). The crude air-dried sulfate weighed 188 g. (theoretical yield).

(Mellon) Anhydrous IV (10 g.) gave 24 g. of crude acid sulfate which was purified by washing with absolute alcohol (125 ml.) and recrystallizing the washed product (20 g.) from absolute alcohol (600 ml.). The material was obtained as golden-yellow crystals (14.6 g.), m.p. 249–250°. Although this salt has been described before (5) there is no indication in the literature whether it is the acid or normal sulfate. Analysis showed it to be the acid sulfate.

Anal. Calc'd for $C_{18}H_{15}NO \cdot H_2SO_4$: N, 3.90; S, 8.93.
Found: N, 3.83; S, 8.95.

The crude sulfate was transformed to free base by shaking with excess 20% sodium hydroxide and extracting with ether (chloroform has some advantages as the extractant). Usually the product was obtained as a greenish solid, sometimes as an oil. Purification of the styryl compound from ligroin was tedious and attended by considerable loss but the crude material could be used in the next step. The yield was usually about 85–90%, but occasionally fell to 65%. When 10-g. portions of anhydrous IV were treated as described by Rabe, the yield of styryl base was 13.7 g. (94%) (R.S.T. and M.A.C.).

Procedure B (Mellon). The method was improved by omitting isolation of the acid sulfate, giving 6-methoxy-4-styrylquinoline directly. Distilled anhydrous 6-methoxylepidine (20 g.) was condensed with benzaldehyde as described above, the cooled reaction mixture dissolved in 150 ml. of chloroform and extracted with two 100-ml. portions of 8 *N* sodium hydroxide solution. The chloroform solution was dried and evaporated to dryness under diminished pressure, giving 127 g. of a greenish-brown liquid which was freed from benzaldehyde (89 g.) by distillation at 20 mm.; a second fraction (5 g. of yellow, somewhat viscous liquid, probably containing 6-methoxylepidine) distilled at 94–98° at 0.05 mm. (bath temp. 124–180°). The dark green still residue (33.5 g.) was dissolved in 150 ml. of chloroform and extracted with 75 ml. of 8 *N* sodium hydroxide solution, washed with water, dried, and evaporated to dryness; yield 27.2 g. For purification, this was dissolved in 408 ml. of boiling heptane under reflux, the hot solution decanted through a fluted filter to remove a trace of insoluble gum, and the filtrate allowed to cool to room temperature; a further small amount of dark-colored gum separated. The yellow heptane solution was decanted, nucleated, and kept overnight in the refrigerator, giving a first crop (10.6 g.) of yellow crystals; m.p. 59–60° (free base). Further crops were isolated from the mother liquor, and by retreatment of the gum.

It was recrystallized as follows: 10 g. was dissolved in 100 ml. of dry ether, 200 ml. of pentane was added, and the mixture filtered, nucleated, and kept overnight in the refrigerator, giving a first crop (6.3 g.) of extremely pale yellow crystals, m.p. 63–64°. Again recrystallized, it had m.p. 64–65°. [Rabe (5) gives m.p. 75°, possibly a misprint.]

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.72; H, 5.8; N, 5.36.
Found: C, 82.51; H, 5.8; N, 5.36.

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[8]When the reaction was carried out at 140° for 19 hours, the yield was only 20%.

Condensation of 6-methoxylepidine with benzaldehyde in acetic anhydride (Columbia, Merck). A solution of 10 g. of 6-methoxylepidine hydrate, 6.0 g. of benzaldehyde, and 43.2 g. of acetic anhydride was boiled under reflux for 4 hours, the mixture evaporated to dryness under reduced pressure, the residue mixed with 5 *N* sulfuric acid, and the styryl sulfate isolated as described above. The yield was only 41% of the theoretical.

Quininic acid (VI) Procedure A. By proceeding essentially as described by Ainley and King (1), using 50% pyridine as solvent *and* for washing the manganese oxides, the highest yield of acid was 95% (Mellon), while the average yield was 70–85%. The variations in yield were probably due to variations in purity of the crude styryl base used. In larger runs (180 g. of styryl compound) the time of reacting was increased to 6 hours. There was no indication that the use of stoichiometric amounts of permanganate gave better yields than the use of the ratio prescribed by Ainley and King (1).

Procedure B (Columbia). When the above procedure was followed, but using acetone as solvent instead of 50% pyridine, the yield of quininic acid was about the same (75–85%). Acetone has certain advantages as the solvent: (a) The manganese dioxide is more easily removed; when 50% pyridine is used a difficultly-filterable sludge is obtained; (b) the acetone is more readily removed from the product than is the pyridine-water mixture; and (c) acetone is considerably cheaper than pyridine.

Ethyl quininate (VII) (Columbia). The procedure of Ainley and King was followed, but the ester was purified by crystallization instead of by distillation. A solution of the crude, dry ester (101 g. from 94.5 g. of quininic acid) in hot 90–110° ligroin (450 ml.) was stirred with Norit, the mixture filtered, and the Norit rinsed with 50 ml. of hot solvent. When the filtrate was cooled slowly to 4° there precipitated 83.6 g. of light cream-colored ester, m.p. 66–67.5°. Concentration of the filtrate gave a second crop (6.0 g.) with the same melting point. The yield was 84%; if this is corrected for the 5 g. of quininic acid recovered from the ammoniacal washings, the yield is raised to 90%.

Pilot-plant runs (Merck and Co.). The *p*-acetoacetanisidide (I) was prepared by U.S. Industrial Chemicals, Inc., at our request. The product supplied by them was gray-white in color, and melted at 115–116°; it was suitable for use without purification.

In the ring-closure reaction (I → II) a 57-lb. run was carried through, using procedure B. The reaction was performed in a 10-gallon Pfaudler jacketed reactor, fitted for steam or brine, and having an efficient agitator. The yield of light gray II, m.p. 259–266° (dec.), which was thoroughly washed and dried but not recrystallized, was 78%.

When 15–20 lb. batches of II were converted to III by the B procedure (with isolation by procedure A), the yield of unrecrystallized III was 85–90%. The chlorination was carried out in a stainless steel reaction vessel provided with hot or cold jacket, and the mixture was stirred during the reaction with an "anchor" type stirrer. Recrystallization of the crude product from 95% alcohol led to a poor recovery (62.2%), making the yield of pure III about 54%.

The chlorine was removed from III by catalytic hydrogenolysis over Raney nickel, as described in Procedure A, using 12–15.5 lb. batches of III. The reactor was stainless steel and was equipped with a very vigorous agitator. The conversion of III to 6-methoxylepidine monohydrate (IV) gave an average yield of 87.3%.

The 6-methoxylepidine was condensed with benzaldehyde, as described in Procedure A, using 10–12 lb. batches of IV. In one case the yield of crude styryl compound (V) was 78%; in another, 89%. The reactions were carried out in a stainless steel oil-heated still provided with a stainless steel stirrer, and a slow stream of nitrogen was passed through the hot solution for the entire 6.5-hour reaction period. No rubber or neoprene gaskets could be used because they were attacked by the benzaldehyde vapors. The free styryl base was liberated as described in Procedure A, as much ether as possible was removed, and then a current of nitrogen under reduced pressure was pulled through the residue at 100° for one hour, in order to remove all volatile material. The crude residue was used, without purification, in the oxidation step.

The large-scale oxidation work was carried out before the acetone procedure (Procedure

B) had been developed and, consequently, 50% pyridine was used as solvent. When a 27-lb. batch of styryl compound was used, the reaction time was nine hours; the manganese dioxide sludge was removed through a small filter press, and the filter cake was slurried twice with 20 to 25 gallon portions of water to ensure complete removal of the quininic acid. The quininic acid, dried to constant weight at 40–50° under reduced pressure, was obtained in 103% yield. This material showed a neutralization equivalent of 232, whereas the calculated value is 210.

Large-scale esterification of the quininic acid (VI → VII) (22.27 lbs. of quininic acid and 18 gallons of absolute alcohol) gave but a poor yield of ester (53%, corrected for recovered quininic acid).

SUMMARY

Simplified and improved procedures for the preparation of ethyl quininate from *p*-anisidine are described. The over-all yield has been increased some 63%.

Methods of purifying the intermediates are given and their correct melting points are recorded.

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