Synthesis of 5,6,7-Trimethylbenz[*c*]acridine

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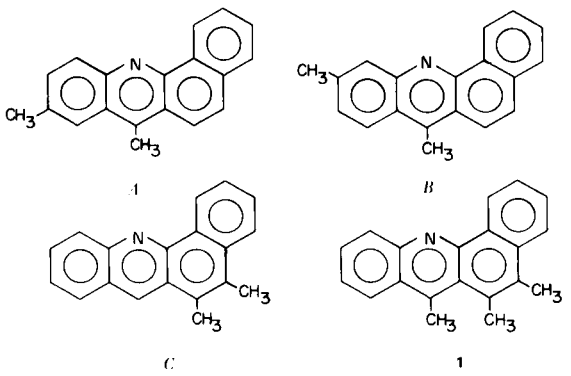
A new potential carcinogenic aromatic heterocyclic compound, 5,6,7-trimethylbenz[c]acridine (**1**), has been synthesized from the known 5,5-dimethyl-6-keto-5,6-dihydrobenz[c]acridine (**4**) using a series of reactions which includes an interesting new type of 1,4-conjugate addition employing lithium dimethylcopper.

As part of a continuing program involving the synthesis of carcinogenic benzacridines and related compounds we became interested in the synthesis of the new 5,6,7-trimethylbenz[c]acridine (**1**). This compound combines the structural features which are present in several very active carcinogens (1), namely, *A* 7,9-, *B* 7,10- and *C* 5,6-dimethylbenz[c]acridine.

Although several synthetic pathways were considered, the most promising route involved the alkylation of the known (2) 5,5-dimethyl-6-keto-5,6-dihydrobenz[c]acridine (**4**). A necessary precursor to the desired ketone **4** was the available 5,5-dimethyl-5,6-dihydrobenz[c]acridine (**2**). Although the existing method for producing this material was satisfactory a more convenient procedure for its synthesis was developed. The use of stannous chloride reduction of nitroketones has been employed (3) in the synthesis of various amino ketones. This reaction has usually been performed in acidic aqueous medium and the compound freed from the tin complex by basic hydrolysis. In the procedure devised by us the nitroketone was added to a solution of stannous chloride in acetic acid which was saturated with hydrogen chloride. After the initial exothermic reaction the solution was refluxed for several hours. Upon cooling the tin complex separated from solution and was filtered. Hydrolysis of the complex was accomplished by the addition of alcoholic potassium hydroxide to a suspension of the complex in refluxing ethanol. The resulting mixture was filtered and diluted with water to afford compound **2**. This procedure gave consistently good yields, regardless of the scale of the reaction, of pure material.

This reduction procedure should prove useful in the synthesis of other heterocyclics, such as benz[*b*]acridines (4) and indenoquinolines (5), which are formed from similar starting materials.

(Scheme I)

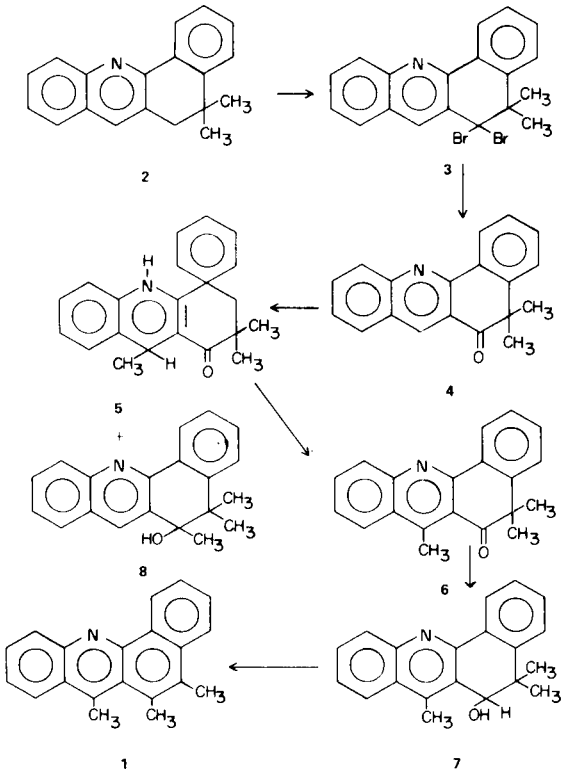


With the necessary starting material in hand we concerned ourselves with securing an alternate pathway to the key compound in our projected synthetic scheme. The previously reported procedure for the formation of ketone **4** involved bromination of compound **2**, followed by hydrolysis of the bromide and oxidation to the corresponding ketone. This route was shortened to two steps and the yield increased (from 55% to 85%) for the conversion of dihydro compound **2** to ketone **4**. The manner in which this was accomplished was to first convert the dihydro compound **2** to the dibromide **3** through the use of 2.3 equivalent of *N*-bromosuccinimide followed by direct conversion to the ketone employing base hydrolysis.

A consideration of the sequence of reactions involved in the transformation of dihydrobenz[c]acridine into 5,6-dimethylbenz[c]acridine led to the observation that if 5,5,7-trimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (**7**) could be obtained it could readily be converted to the desired compound **1**.

The key step then became the introduction of the methyl group into the 7-position of ketone **4**. In view of the work of Fuson and Miller (6) which demonstrated that

(Scheme II)



phenyl magnesium bromide would add 1,4- to the quinoline nucleous of 3-benzoylquinoline, it was hoped that a similar reaction would occur with methyl magnesium bromide in the case of the benzacridine ketone.

Thus when methyl magnesium iodide was permitted to react with the ketone only a white crystalline product was obtained (9). The nmr spectrum of a deuterochloroform solution of this material revealed the presence of three methyl groups as singlets. This material is clearly the carbinol **8** which arises by 1,2-addition to the ketone. When the reaction was carried out at -78° with methyl lithium two products were formed. The nearly identical behaviour on thin layer chromatography plates prevented their ready separation using this method. However, it was clear from the nmr spectrum of the mixture and the tlc data that the 1,2-addition product **8** greatly predominates.

In view of our recent success in effecting the conjugate addition of lithium dimethyl copper to heterocyclic ketones we employed the reagent on this substrate (7). Thus, when a solution of lithium dimethyl copper (8) was treated with an ethereal solution of the ketone **4** a reaction occurred with the precipitation of presumably methyl copper (8). The reaction was worked up by the cautious addition of first methanol and then water to afford an ether layer which contained starting material and carbinol as well as an additional product. Two recrystallizations of this mixture from heptane-benzene served to remove unreacted starting material and the alcohol **8**. In this fashion there was also obtained a yellow crystalline product. The nmr spectrum of this material revealed two equivalent methyl groups as well as a third which appeared as a doublet. (J = 7 cps). The 7-proton was evident as a quartet (J = 7 cps). Thus the 1,4-addition product **5** was obtained in pure form.

The precipitate which formed when the ketone **4** was added to the solution of reagent was initially presumed to be methyl copper. However, thin layer chromatography of the supernatant liquid in the reaction mixture revealed the presence of mainly unreacted ketone **4** and carbinol **8** with very little of the 1,4-addition product **5** present. When a portion of the precipitated solid was filtered, washed with anhydrous ether, and hydrolyzed with methanol the predominent product found was the vinylogous amide **5**. Accordingly the reaction mixture was filtered and the precipitate washed with ether. Hydrolysis of this material afforded nearly pure 1,4-addition product **5** in a moderate yield.

In order to complete the synthesis of the target compound **1** the 1,4-addition product **5** was oxidized with choranil to afford the trimethyl ketone (6). This ketone was reduced with sodium borohydride to afford the precursor alcohol **7**.

Alcohol **7** was subjected to acid treatment in the manner previously described for the synthesis of 5,6-dimethylbenz[c]acridine (2). It is noteworthy that the rearrangement is best effected by slow addition of the finely powdered alcohol to the sulfuric acid. Further work aimed at the synthesis of other 7-substituted dimethylbenz[c]acridines is in progress and will be reported in due course.

EXPERIMENTAL

Preparation of 5,5-Dimethyl-5,6-dihydrobenz[c]acridine (**2**).

A mixture of glacial acetic acid (250 ml.) and stannous chloride (stannous chloride dihydrate, 178.5 g., 0.79 mole) was saturated with hydrogen chloride gas until a turbid solution resulted. The addition of 4,4-dimethyl-2-(*o*-nitrobenzal)-1-tetralone (2) (60 g., 0.195 mole) initiated an exothermic reaction. After the reaction subsided the solution was heated at reflux for 12 hours as hydrogen chloride was slowly bubbled through the solution. The solution was permitted to cool whereupon a yellow solid precipitated from the orange colored mixture. The mixture was filtered to remove the solid which was washed with a little cold acetic acid and cold ether to afford the tin complex (90 g.). The tin complex was suspended in refluxing ethanol (1500 ml.) and a solution of potassium hydroxide in ethanol (65 g. in 650 ml.) was slowly added. The color of the mixture turned from pale yellow to milky white to pale yellow signifying that the hydrolysis of the tin complex was complete. The mixture was filtered (celite pad) to remove the inorganic material and the filtrate was concentrated (one liter). The alcohol solution was diluted with water (one liter) and chilled to 0°. The pale white crystals were removed by filtration to give the product (40 g., 80%) identical with material prepared by Bell and

Cromwell (2); nmr (deuteriochloroform): δ 1.30 (s, 6H, CH_3-5), 2.67, (s, 2H, H-6), 7.3-7.9 (m, 6H, arom), 7.85 (s, 1H, H-7), 8.15 (m, 1H, H-11), 8.65 (m, 1H, H-1).

6,6-Dibromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**3**).

To a solution of **2** (39.5 g., 0.15 mole) in carbon tetrachloride (600 ml.) was added freshly recrystallized dry *N*-bromosuccinimide (60 g., 0.34 mole). The mixture was heated for 1.5 hours by heat provided by a 500 watt sun lamp. After chilling the succinimide was removed by filtration. The filtrate was evaporated to afford pale yellow crystals of product (62.5 g., 100%). A portion of this material was recrystallized from heptane to afford white crystals of the product **3** (m.p. 187-189°); nmr (deuteriochloroform): δ 1.25 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 7.4-8.3 (m, 6H, arom), 8.12 (m, 1H, H-11), 8.68 (m, 1H, H-1), 8.92 (s, 1H, H-7).

Anal. Calcd. for $C_{19}H_{15}Br_2N$: C, 54.70; H, 3.63; N, 3.36. Found: C, 54.85; H, 3.62; N, 3.40.

5,5-Dimethyl-6-keto-5,6-dihydrobenz[c]acridine (**4**).

The dibromide **3** (60 g., 0.14 mole) was dissolved in aqueous methanol (3%, 600 ml.) and heated at reflux for 7 hours. The solution was made basic with the minimum amount of potassium hydroxide solution (50%). The volume of the solution was reduced to 300 ml. by roto-evaporation. Water (100 ml.) was added and roto-evaporation was continued until the product crystallized from solution. More water was added and the mixture was filtered to remove the ketone **4** (37 g., 93%, m.p. 80°). Recrystallization of this product from aqueous ethanol afforded material of higher purity (34.5 g., 88%, m.p. 89-90°; lit. (1) m.p. 89-90°); nmr (deuteriochloroform): δ 1.62 (s, 6H, CH_3), 7.35-8.10 (m, 6H, arom.), 8.15 (m, 1H, H-11), 8.88 (m, 1H, H-7), 8.92 (s, 1H, H-1).

Reaction of Ketone **4** with Lithium Dimethylcopper.

To a solution of lithium dimethylcopper (from 3.8 g., 20 mmoles of cuprous iodide and approximately 26 ml. of 1.5 *M* methyllithium) at 0° was added an ethereal solution of the ketone **4** (3.8 g., 14 mmoles in 75 ml.) over a period of 2 hours. After the addition was complete stirring was continued at 0° for 1 hour and at room temperature for 1 hour. The resulting mixture was filtered to remove the yellow solid which was washed with dry ether. The yellow solid was transferred to a beaker and decomposed by the addition of methanol. The mixture was then evaporated to dryness and partitioned between ether and water (100 ml./100 ml.). The ether layer was separated and the aqueous layer was extracted further with ether (2 x 50 ml.). The combined ether extracts were washed with water, saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The ether solution was evaporated to dryness to afford the yellow product **5** (2.5 g.). This material could be obtained in an analytically pure form by recrystallization from benzene-heptane solution (2.2 g., 54% m.p. 214-215°). The ether solution from the reaction mixture contained traces of the 1,4-addition product **5**, as well as, 1,2-addition product (**8**) (0.67 g., 16%, m.p. 115-116°, see below) and some starting material (0.44 g.); nmr of 6-keto-5,5,7-trimethyl-5,6,7,12-tetrahydrobenz[c]acridine (**5**) (deuteriochloroform): δ 1.25 (d, 3H, CH_3-7m J = 7 cps), 1.47 (s, 3H, CH_3-5), 1.57 (s, 3H, CH_3-5), 4.39 (q, 1H, H-7, J = 7 cps), 7.0-7.82 (m, 8H, arom); nmr of 6-hydroxy-5,5,6-trimethyl-5,6-dihydrobenz[c]acridine (**8**) (deuteriochloroform): δ 1.08 (s, 3H, CH_3-5), 1.35 (s, 3H, CH_3-6), 1.55 (s, 3H, CH_3-5), 2.10 (s, 1H, OH), 7.38-7.98 (m, 6H, arom), 8.22 (1H, H-11), 8.42 (s, 1H, H-7), 8.63 (m, 1H, H-1).

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found for **5**: C, 82.69; H, 6.30; N, 4.85.

Reaction of Ketone **4** with Methylmagnesium Bromide.

To a solution of 0.51 g. (0.002 mole) of ketone **4** in 25 ml. of dry ether was added 20 ml. (0.06 mole) of a 3 *M* solution of methylmagnesium bromide in 10 ml. of dry ether. After stirring for several minutes, the reaction mixture was decomposed by the addition of saturated ammonium sulfate solution. The resulting mixture was thoroughly extracted with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the solid residue (**8**) was crystallized from benzene to give 0.55 g. (quantitative) of white needles, m.p. 113.5-116°; λ max (218), 226, (259), 267, 300, 316, 330, 345 mμ (ε, 19,000, 19,500, 20,300, 21,500, 7,450, 9,800, 11,000); (carbon tetrachloride): γ_{OH} 3600/16, γ_{CH} 3072/32, 3042/33, γ_{CH_3} 2980/46, $\gamma_{C=C}$ and $_{C=N}$ 1623/22, 1603/24, 1502/35, 1488/40.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.31; H, 6.74; N, 4.77.

6-Keto-5,5,7-trimethyl-5,6-dihydrobenz[c]acridine (**6**).

A chloroform (300 ml.) solution of the 1,4-addition product **5** (4.0 g., 13.8 mmoles) and chloranil (5 g., 20 mmoles) was heated at reflux for 6 hours. The chloroform solution was extracted with 10% sodium hydroxide solution (3 x 100 ml.) and washed with water. After drying with anhydrous magnesium sulfate the chloroform was evaporated to afford a colorless oil (3.7 g.). One recrystallization of this material from ethanol with charcoaling afforded white crystals of the trimethyl ketone **6** (3.16 g., 80%, m.p. 127-128.5°); nmr (deuteriochloroform): δ 1.56 (s, 6H, CH_3-5), 2.96 (s, 3H, CH_3-7), 7.4-8.3 (m, 6H, arom), 8.83 (m, 1H, H-1).

Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.39; H, 5.88; N, 4.89.

6-Hydroxy-5,5,7-trimethyl-5,6-dihydrobenz[c]acridine (**7**).

To a solution of the trimethylketone **6** (2.77 g., 9.65 mmoles) in diglyme (120 ml.) at 50° was added sodium borohydride (1 g., 26 mmoles). The yellow solution was heated for 18 hours after which time it appeared colorless. The reaction mixture was quenched by pouring it into saturated ammonium chloride solution (400 ml.). The white precipitate was removed by filtration, washed well with water and dried to afford the product (2.70 g., 97%, m.p. 214.5-219°). Two recrystallizations from methanol afforded an analytically pure sample (m.p. 216-219°); nmr (deuteriochloroform): δ 1.00 (s, 3H, CH_3-5), 1.70 (s, 3H, CH_3-5), 1.80 (s, 1H, OH), 2.78 (s, 3H, CH_3-7), 4.90 (s, 1H, H-6), 7.38-8.34 (m, 7H, arom), 8.65 (m, 1H, H-1).

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.81; H, 6.55; N, 4.86.

5,6,7-Trimethylbenz[c]acridine (**1**).

A finely powdered sample of the trimethyl alcohol **7** (2.0 g., 6.9 mmoles) was added in portions to well-stirred cold sulfuric acid (95%, 50 ml.). After 2 hours the sulfuric acid solution was poured over a mixture of ice and concentrated sodium hydroxide (50%, 200 ml.). The resulting mixture was extracted with chloroform (4 x 200 ml.). The combined extracts were dried over anhydrous magnesium sulfate and evaporated to afford the crude product (1.6 g.). After recrystallization from ethanol **1** was obtained as a crop of fine yellow needles (1.2 g., 64%, m.p. 139-141°); nmr (deuteriochloroform): δ 2.55 (s, 3H), 2.63 (s, 3H), 3.00 (s, 3H, CH_3-7), 7.4-8.4 (m, 7H, arom), 9.50 (m, 1H, H-1).

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16. Found: C, 88.31; H, 6.24; N, 5.21.

REFERENCES

(1a) N. H. Cromwell, *American Scientist*, 53, 213 (1965); (b) A. Lacassagne, N. P. Buu-Hoi, R. Daudel and F. Zazdela, *Adv. Cancer Res.*, IV, 315 (1956).

(2) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, 23, 789 (1958).

(3) R. B. Woodward, *Org. Syn., Coll. Vol.*, 3, 453 (1955).

(4) N. H. Cromwell and J. C. David, *J. Am. Chem. Soc.*, 82, 1138 (1960).

(5) N. H. Cromwell and R. A. Mitsch, *J. Org. Chem.*, 26, 3812, 3817 (1961).

(6) R. C. Fuson and F. A. Miller, *J. Am. Chem. Soc.*, 79, 3478 (1957).

(7) N. H. Cromwell and D. J. Pokorny, *J. Heterocyclic Chem.*, 12, 533 (1975).

(8) H. O. House, W. L. Respress, and George M. Whitesides, *J. Org. Chem.*, 31, 3128 (1966).

(9) L. A. Nielsen, Ph.D. Thesis, University of Nebraska, (1962), page 25.