Synthesis of 5,6-Dimethylbenz[*a*]phenazine

N. H. Cromwell, H. S. Desai and D. J. Pokorny

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

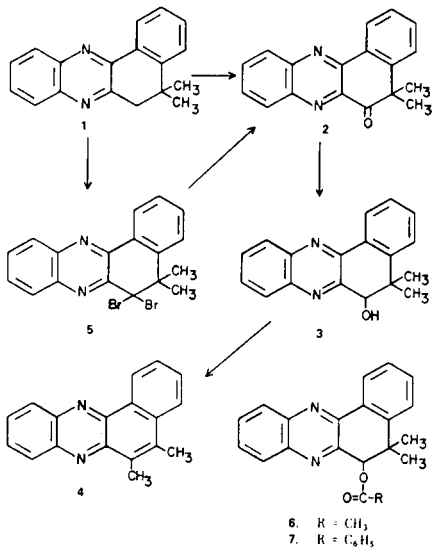
Received May 7, 1976

5,6-Dimethylbenz[*a*]phenazine (**4**), an aza analogue of the carcinogenic 5,6-dimethylbenz-[*c*]acridine has been obtained by a 1,1-dehydration-rearrangement (Wagner-Meerwin type) from 5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[*a*]phenazine (**3**). The alcohol **3** was obtained from the hydrogenation of the corresponding ketone **2** which was prepared in two ways: Method A, the oxidation of 5,5-dimethyl-5,6-dihydrobenz[*a*]phenazine (**1**); Method B, the hydrolysis of the 6,6-dibromo derivative **5** of **1**.

J. Heterocyclic Chem., 13, 945 (1976).

Results and Discussion

As part of studies aimed at the synthesis of carcinogenic compounds we became interested in the synthesis of 5,6-dimethylbenz[*a*]phenazine (**4**) (1). This compound can be viewed as an aza analogue of 5,6-dimethylbenz[*c*]-acridine which has been found to show carcinogenic activity on the skin of inbred strains of mice (1). Another literature report describes the synthesis of this compound although in low yield (2). The only other literature reports that describe a compound which might yield the desired material are the report of the synthesis of 5,5-dimethyl-5,6-dihydrobenz[*a*]phenazine (**1**) (3) and the synthesis and reactions of 6,6-dimethyl-5,6-dihydrobenz-[*a*]phenazine (4).



Our initial approach was modeled after the successful synthesis of 5,6-dimethylbenz[*c*]acridine (5). This procedure involved the free radical bromination of 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine to yield the 6-bromo 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. This bromo compound was hydrolyzed in alkaline water-dioxane mixture to the corresponding alcohol. Subsequent treatment of this alcohol with concentrated sulfuric acid gave the aromatized compound (6). Thus the readily available dihydro compound **1** brominated to afford the 6-bromo-5,6-dimethyl-5,5-dihydrobenz[*a*]phenazine. Attempts at converting this material to the corresponding alcohol met with marginal success. Frequently, the alcohol was formed in low yield as part of a four component mixture.

Another approach taken from work done by this group with the indeno[1,2-*b*]quinoline series (7) was applied with more success. Thus chromium oxide oxidation of the dihydro compound afforded the corresponding 6-keto-5,6-dimethyl-5,6-dihydrobenz[*a*]phenazine (**2**). It was subsequently observed that the dibromide **5** obtained from the bromination of dihydro compound **1** could be hydrolyzed in acid media (see experimental) to produce the ketone **2**. This ketone was reduced under carefully controlled conditions with sodium borohydride. The conditions necessary to permit ready filtration of the product eliminated contamination with a yellow compound that formed in the reduction step. This was necessary to insure high purity of the alcohol **3**.

Alcohol **3** exhibited a tendency to be converted to the ketone on heating in air. When the alcohol was heated in the melt for 80 minutes at 160° and the resulting mixture was dissolved in deuteriochloroform with the exclusion

of oxygen the sample was a very dark blue in color and its nmr spectrum revealed the presence of the alcohol, traces of the ketone and another compound which displayed a singlet in the methyl region at δ 1.48, broad peaks at δ 5.28 and 5.67, and a complex multiplet centered at δ 6.35. These solutions became yellow in color upon the admission of air and the signals due to the latter compound disappeared with a concurrent increase in the signals due to the ketone. Studies are underway to determine the exact nature of this intermediate. The spectrum of a sample which had been heated at 160° for seven hours revealed that the alcohol had converted to a mixture of the dihydro compound **1** and the ketone 2. Treatment of the alcohol **3** with concentrated sulfuric acid in a manner similar to that described by Cromwell and Nielson for the formation of 5,6-dimethylbenz[*c*]-acridine (6) afforded a mixture of two products. The reaction time had to be increased to several hours since working for shorter periods of time returned a large amount of starting material. These two products were found to be 5,5-dimethyl-5,6-dihydrobenz[*a*]phenazine (**1**) and 5,6-dimethylbenz[*a*]phenazine (**4**). In some cases, these proved to be separable by extracting the completely aromatic compound away from the sulfuric acid salt of the dihydro compound. This procedure, however, is difficult to repeat consistently. Alcohol **3** reacted normally with acetic anhydride to produce the expected 6-acetoxy derivative **6** and with benzoyl chloride to give the corresponding benzoyloxy derivative, **7**.

The formation of the dihydro compound is an interesting anomaly. Care was taken to employ alcohol of the highest purity in these reactions. Thus no ketone or dihydro compound were observed in the starting material. However, when the sulfuric acid solution of the alcohol was worked up after short reaction times, a mixture consisting of largely starting material was obtained. An nmr spectrum of this mixture revealed the presence of three minor components: the completely aromatic phenazine, the ketone, and the dihydro compound in a ratio of: (2:2:1). The dihydro compound was stable in sulfuric acid solution. None of the ketone could be observed in the reaction mixtures which were allowed to proceed longer than 2 hours. Thus if ketone is formed under these conditions it is decomposing in the media.

The problem of low yields, irreproducibility and formation of mixtures led us to seek an alternate approach for the aromatization-dehydration step. In this regard, polyphosphoric acid was employed as a reaction medium. However, a mixture of dihydro compound and aromatized phenazine was obtained. This difficulty was successfully overcome by employing fuming sulfuric acid as the agent. Use of this reagent allowed the speedy formation of almost exclusively the desired compound **4** in excellent yield. The properties of this material agreed closely with those reported for the product isolated from the reaction of 2-ethyl-1,4-naphthaquinone with *o*-phenylenediamine (2).

EXPERIMENTAL

5,5-Dimethyl-5,6-dihydroben[*a*]phenazine (**1**).

An ethanol solution containing 1,2-dioxo-4,4-dimethyltetraline (3) (7.47 g., 39.7 mmoles) and freshly sublimed *o*-phenylenediamine (4.3 g., 39.8 mmoles) was heated at reflux for ten hours. The ethanol was removed under vacuum and the resulting solid was redissolved in benzene (100 ml.). This benzene solution was passed through an alumina column (50 g., Woelm, Grade I) and the eluant collected. The first two fractions (300 ml.) contained the product **1** (10.3 g., 91%, m.p. 114-115°, lit. (3) m.p. 114.5-116°). If impure ketone or unsublimed amine were employed the product was invariably pale yellow instead of white; nmr (deuteriochloroform): δ 1.38 (s, 6H, CH_3), 3.24 (s, 2H, CH_2), 7.37-7.84 (m, 5H, arom.), 8.27 (m, 2H, H-8 and H-11), 8.59 (m, 1H, H-1).

5,5-Dimethyl-6-keto-5,6-dihydrobenz[*a*]phenazine (**2**). Method A.

A solution of chromium trioxide (5 g., 50 mmoles) in 80% acetic acid (20 ml.) was added dropwise to a refluxing solution of the dihydro compound **1** (3.25 g., 125 mmoles) in acetic acid (40 ml.). The reaction mixture was heated for 8 hours, permitted to cool, and stirred overnight. The reaction was hydrolyzed by pouring onto a mixture of ice and sodium hydroxide solution. The resulting mixture was extracted with ether (5 x 100 ml.). The combined ether extracts were dried over anhydrous sodium sulfate and evaporated to afford the crude product (2.5 g.). This material was recrystallized from aqueous ethanol to afford pale green crystals (2.1 g., 61%, m.p. 157-159°); nmr (deuteriochloroform): δ 1.66 (s, 6H, CH_3), 7.45-8.5 (m, 7H, arom.), 8.77 (m, 1H, H-1); ir (Nujol): ν C=O = 1700 cm^{-1}; uv (methanol): λ max, 220, 227, 258, 278, 342, 365 nm (ε max, 17,700, 16,300, 17,000, 20,200, 4,390, 4,480).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.85; H, 5.09; N, 10.13.

6,6-Dibromo-5,5-dimethyl-5,6-dihydrobenz[*a*]phenazine (**5**).

N-Bromosuccinimide (3.923 g., 22 mmoles) was added to a solution of the dihydro compound **1** (2.26 g., 8.7 mmoles) in carbon tetrachloride (150 ml.). The resulting mixture was heated by the warmth of a 500 watt sun lamp. After 35 minutes at reflux the tlc (silica gel; 1:1; carbon tetrachloride-hexane) revealed that all of the starting material had been converted to the product. The unreacted NBS and succinimide were removed by filtration. The filtrate was evaporated to give an oil. This oil was dissolved in hot hexane (100 ml.), charcoaled, filtered and concentrated. In this fashion the pure material was obtained (2.9 g., 80%, m.p. 146-148°); nmr (deuteriochloroform): δ 1.27 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 7.35-7.90 (m, 5H, arom.), 8.17 (m, 2H, H-8 and H-11), 8.60 (m, 1H, H-1).

Anal. Calcd. for $C_{18}H_{14}Br_2N_2$: C, 51.70; H, 3.37; N, 6.70. Found: C, 51.53; H, 3.52; N, 6.58.

Phenazine 2, Method B.

To a solution of the dibromide **5** (2.35 g., 5.62 mmoles) in hot methanol (200 ml.) was added 30% hydrobromic acid in acetic acid (4 ml.) and water (8 ml.). After heating at reflux for 3 days water and bicarbonate solution were added and the methanol was removed on the rotoevaporator. In this way the product **2** was obtained (1.6 g., 68%).

5,5-Dimethyl-6-hydroxy-5,6-dihydrobenz[*a*]phenazine (**3**).

Sodium borohydride (1.2 g., 31.2 mmoles) was added in small portions to a solution of the ketone **2** (4 g., 14.6 mmoles) in isopropyl alcohol (175 ml., dried by passing through Grade I alumina, Woelm) at room temperature. Although the reaction was complete in thirty minutes the product had just started to precipitate from solution. After one hour at room temperature the reaction mixture was stored at -15° for 4 hours. The solid material that precipitated was removed by filtration and dried to afford a white solid (3.9 g.). This material was dissolved in chloroform and passed through a short silica gel column (3 inch) to remove some inorganic salts. The chloroform solution from the column was evaporated to afford a white solid which was pure alcohol **3** (3.1 g., 77%). A portion of this material was recrystallized from absolute alcohol to afford an analytically pure sample of the alcohol **3** (m.p. 149-150°); nmr (deuteriochloroform): δ 0.98 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 4.82 (s, 2H, H-6 and OH), 7.40-7.9 (m, 5H, arom.), 8.08 (m, 2H, H-8 and H-11), 8.55 (m, 1H, H-1); ir (carbon tetrachloride): ν OH = 3480 cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.06; H, 5.68; N, 9.90.

Formation of 5,6-Dimethylbenz[*a*]phenazine (**4**) Employing 95% Sulfuric Acid.

The precursor alcohol **3** (2.25 g., 8.1 mmoles) was added in small portions to sulfuric acid (95%, 50 ml.) at room temperature. After complete dissolution of the alcohol, the solution was heated at 80° for five hours. The solution was poured into water (300 ml.) and chilled overnight (0°). The orange solid was partitioned between warm base (sodium hydroxide, 1%, 50 ml.) and refluxing chloroform (200 ml.). The mixture was filtered and the residue was washed with chloroform. The chloroform layer was separated, dried, and evaporated to a small volume (50 ml.). This solution was passed through an alumina column (Woelm, Grade I; 50 g.) and the column eluted with chloroform. The first fraction (200 ml.) was evaporated to dryness to afford 5,6-dimethylbenz[*a*]phenazine (1.57 g., 75%, m.p. 165°). One recrystallization from aqueous alcohol afforded an analytically pure sample (m.p. 169°, lit. (2) 163-164°). The filtrate from the reaction mixture after treatment with base and extraction with chloroform afforded a sample of the 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. This procedure although workable sometimes afforded mixtures which were separable with difficulty.

Formation of 5,6-dimethylbenz[*a*]phenazine (**4**) Employing 15% Fuming Sulfuric Acid.

The finely powdered alcohol **3** (4.0 g., 14.5 mmoles) was added slowly in portions to sulfuric acid (50 ml., 15% sulfur trioxide). After 0.5 hour the black solution was poured over a mixture of crushed ice (1 kg.) and base (200 ml. of 25% sodium hydroxide). The resulting mixture was extracted with chloroform (3 x 200 ml.). The combined chloroform solutions were washed with water, dried and evaporated to afford the crude product (3.6 g.). Recrystallization from absolute alcohol afforded analytically pure material (3.4 g., 90%, m.p. 169-170°); nmr (deuteriochloroform): δ 2.58 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 7.5-8.1 (m, 5H, arom.), 8.20 (m, 2H, H-8 and H-11), 9.30 (m, 1H, H-1); ir (carbon tetrachloride): ν = 3060, 2960, 1490, 1365 cm^{-1}; uv (methanol): λ max, 206, 220, 270, 286, 370, 387, 405 nm (ε max, 44,800, 52,600, 57,900, 54,200, 9,320, 10,700, 10,250).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.77; H, 5.55; N, 11.02.

Picrate of **4**.

Orange yellow needles were obtained from ethanol, m.p. 198-199°.

Anal. Calcd. for $C_{24}H_{17}N_5O_7$: C, 59.14; H, 3.52; N, 14.37. Found: C, 59.10; H, 3.43; N, 14.25.

5,5-Dimethyl-6-acetoxy-5,6-dihydrobenz[*a*]phenazine (**6**).

A mixture of phenazine alcohol **3** (0.100 g.), pyridine (3-4 drops) and acetic anhydride (2 ml.) was heated on a steambath for 0.5 hour after which time, the solution was poured into ice-cold water (100 ml.). The gummy brownish white product was washed with water and recrystallized thrice from petroleum ether to give colorless crystals, m.p. 126-127° (0.090 g.); ir (carbon tetrachloride): ν C=O = 1730 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.76; H, 5.80; N, 9.06.

5,5-Dimethyl-6-benzoyloxy-5,6-dihydrobenz[*a*]phenazine (**7**).

A sample 0.100 g. of the alcohol **3** was dissolved in 0.5 ml. of pyridine. Benzoyl chloride (0.5 ml.) was added to the above solution and the mixture heated on a steambath for one hour. The reaction mixture was then poured into ice-cold water (100 ml.). The solid product was filtered, washed with water and dried. The brown solid (0.110 g.) was recrystallized thrice from petroleum ether to give analytically pure white crystals, m.p. 153-154° (0.090 g.); ir (carbon tetrachloride): ν C=O = 1720 cm^{-1}.

Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.92; H, 5.30; N, 7.36. Found: C, 78.93; H, 5.46; N, 7.46.

Acknowledgement.

This investigation was supported by Research Grant CA-02931 from the National Cancer Institute of the U. S. Public Health Service.

REFERENCES AND NOTES

(1) N. H. Cromwell, *Am. Scientist*, **53**, *No. 2*, 213 (1965).

(2) H. Immer, K. Kunesch, J. Polonsky and E. Wenkert, *Bull. Soc. Chim.*, 2420 (1968).

(3) N. H. Cromwell, H. H. Eby, and D. B. Capps, *J. Am. Chem. Soc.*, **73**, 1230 (1951).

(4) C. Broquet and M. J. Bedin, *Comp. Rend.*, **264**, 1505 (1967).

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

(6) N. H. Cromwell and L. A. Nielsen, *J. Heterocyclic Chem.*, **6**, 361 (1969).

(7) B. D. Pearson, R. A. Mitsch, and N. H. Cromwell, *J. Org. Chem.*, **27**, 1674 (1962).