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

INTERACTION OF α-(4-MORPHOLINYL)PROPIOPHENONE WITH POTASSIUM CYANIDE AND AMMONIUM CARBONATE[1]

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In the course of a study of the behavior of four α-(4-morpholinyl)alkyl aryl ketones with a dilute alcoholic solution of potassium cyanide and ammonium carbonate at 60° (1), the anticipated 5-R-5-R′-hydantoins were obtained except in the case of α-(4-morpholinyl)propiophenone (I). In this instance the products were 5-phenylhydantoin (II) and 5-phenyl-5-[1-(5-phenylhydantyl)]hydantoin (III), the latter, in all probability, being formed from the former through oxidation and subsequent condensation. Since I did not yield the anticipated hydantoin under the usual conditions of the Bucherer procedure (2), attempts were made to bring about the desired conversion under other conditions.

Upon studying the behavior of these reactants, but in a closed vessel at 105° a crystalline reaction product separated, and was subsequently identified as 2,5-dimethyl-3,6-diphenylpyrazine (IV) (3, 4, 5); from the reaction solution was isolated another substance, tentatively formulated as the dipeptide of α-aminophenylacetic acid. Also, the reactants were heated in the closed vessel using propylene glycol as the solvent instead of diluted ethyl alcohol (6), but again the chief product isolated was IV although a small amount of III was obtained.

In an endeavor to account for the formation of such varied reaction products, the action of potassium cyanide and ammonium carbonate, independently, on I was investigated. After exposure of I to potassium cyanide in diluted alcohol in a bomb at 105°, about 77% of the ketone could be recovered unchanged, and the chief product of reaction was identified as benzoic acid; a trace of *dl*-mandelic acid was detected (7), also. The effect of ammonium carbonate on I varied with the temperature at which reaction was carried out. Prolonged warming of ammonium carbonate and I in 50% alcohol at 58–60° resulted in the formation of a crystalline product (V) of molecular formula $C_{11}H_{12}N_2$.[3] However, when reaction was carried out at 112–115°, the chief product was IV[4] of formula $C_{18}H_{16}N_2$. Investigation of the mother liquor from recrystallization of IV resulted in the isolation of a very small amount of another product (VI)[3,5] of formula $C_{18}H_{16}N_2$.

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[3] Compound V was subsequently obtained through interaction of an alcoholic ammonia solution with α-bromopropiophenone, and its structure will be discussed later in connection with its relationship to the researches of Kolb (3) and Collet (4).

[4] A plausible explanation of the formation of IV is suggested by some results of Gabriel's (5), who has shown that α-aminopropiophenone hydrochloride in excess alkali forms 1,4-dihydro-2,5-dimethyl-3,6-diphenylpyrazine, which is spontaneously oxidized to IV by exposure to air. Hence, it appears probable that α-(4-morpholinyl)propiophenone undergoes ammonolysis to form α-aminopropiophenone, which then behaves as indicated.

[5] Since V and VI were found to be by-products accompanying the formation of IV, through interaction of α-bromopropiophenone with alcoholic ammonia, the significance of their formation is subordinate in importance to that of IV.

In view of the data obtained in this study, there can be advanced a partial explanation of the failure of α-(4-morpholinyl)propiophenone to form 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin. At 105°, the formation of this hydantoin is precluded by virtue of the instability of the ketone. There is reason to suspect that the dipeptide of α-aminophenylacetic acid was formed from benzaldehyde, originating as an alkaline degradation product of the ketone. Moreover, the instability of I is reflected in the formation from it of IV. However, such instability of I at 60° does not suffice as an adequate explanation of the failure of I to yield the anticipated hydantoin with potassium cyanide and ammonium carbonate. The amount of 5-phenylhydantoin (II) isolated is larger than that attributable to the presence of benzaldehyde resulting from alkaline cleavage of I. Hence, it is plausible to believe that at least some of the desired disubstituted hydantoin was formed from I by interaction with potassium cyanide and ammonium carbonate, but was decomposed subsequently to II.

During this investigation it was necessary to synthesize an authentic sample of 2,5-dimethyl-3,6-diphenylpyrazine (IV). Collet (4) had noted formation of this compound through interaction of α-bromopropiophenone and alcoholic ammonia but did not investigate this reaction further. In a study of the action of ammonia on α-bromo-α-phenylacetone, Kolb (3) succeeded in isolating three bases, in addition to IV; on the basis of analytical data he assigned to these bases the molecular formulas C_9H_9NO, $C_{18}H_{18}N_2$ and $C_{32}H_{36}N_6$, respectively.

Upon reinvestigation in the present study of the preparation of IV by the method of Collet (4), in addition to this pyrazine there were obtained three bases, analytical data for which indicated molecular formulas respectively of $C_{11}H_{12}N_2$ (V), $C_{16}H_{14}N_2$ (VII), and $C_{18}H_{16}N_2$ (VI). Information gathered concerning these bases is as follows:

$C_{16}H_{14}N_2$ (VII). This base was identified as 2,5-diphenyl-4-methylimidazole (7). With the exception of melting point and ease of solubility in hydrochloric acid, the characteristics of this base, in so far as herein noted, are in agreement with those noted by Kolb (3) for his C_9H_9NO compound.

$C_{11}H_{12}N_2$ (V). The properties exhibited by this substance are those recorded by Kolb (3) for the $C_{32}H_{36}N_6$ base; in addition, the melting point of its picrate is in agreement with that reported by Kolb for the picrate of $C_{32}H_{36}N_6$. But our analytical data clearly indicate the $C_{11}H_{12}N_2$ composition. The actual structure of this compound has not been completely established, but it is thought to be 2,4-dimethyl-5-phenylimidazole.

$C_{18}H_{16}N_2$ (VI). The properties found to be characteristic of this compound are those of the $C_{18}H_{18}N_2$ base which Kolb (3) postulated as a dihydro-2,5-dimethyl-3,6-diphenylpyrazine, but which does not correspond to any of the compounds of that structure subsequently prepared by Gabriel (5).[6] Although

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[6] Gabriel pointed out that, because of the ease of oxidation of the dihydropyrazines to the pyrazines, the method of isolation used by Kolb precluded the possibility of the base being a dihydropyrazine. Further, since Kolb had noted the formation of a yellow color when this compound is dissolved in concentrated hydrochloric acid, Gabriel assumed the substance to be impure 2,5-dimethyl-3,6-diphenylpyrazine ($C_{18}H_{16}N_2$). The analytical results obtained in the present investigation indicate the latter formula to be correct.

the formula and general characteristics duplicate those of 2,5-dimethyl-3,6-diphenylpyrazine, the base is shown to be different in that its melting point is lowered considerably when mixed with an authentic sample of IV. Hence, VI more probably is the isomeric 2,6-dimethyl-3,5-diphenylpyrazine.

EXPERIMENTAL

Attempts to prepare 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin. Three grams of ammonium carbonate and 7.7 g. (0.03 mole) of α-(4-morpholinyl)propiophenone hydrochloride (1) were dissolved in 50 cc. of 60% alcohol; the solution was chilled and to it was added 3.9 g. (0.06 mole) of potassium cyanide and the remaining portion of 12.5 g. (0.13 mole) of ammonium carbonate cubes. This mixture was placed in a Pyrex glass liner of a stainless steel bomb and heated at 105° for fifteen hours. After cooling and opening the bomb, a reaction product was obtained by filtration, extracted twice with ether to remove adhering oily material, and then recrystallized from hot alcohol to yield III; m.p. 127° (corr.). The identity of III was confirmed as 2,5-dimethyl-3,6-diphenylpyrazine by comparison with an authentic sample.[7]

Anal. Calc'd for $C_{18}H_{16}N_2$: N, 10.76. Found: N, 10.88.

The filtrate from the reaction mixture was made slightly acidic with hydrochloric acid; a small amount of dark colored amorphous material was separated and discarded. The filtrate was concentrated to about one-fifth of its initial volume and cooled to room temperature; a light tan-colored solid separated and was filtered off. It was soluble both in dilute acid and alkaline solutions, was insoluble in water, and but sparingly soluble in hot alcohol. Treatment with dilute hydrochloric acid left some amorphous material undissolved and treatment of the acidic solution with excess sodium hydroxide produced a further, small amount of amorphous material. Exact neutralization of the filtered basic solution yielded crystalline material which was digested with hot alcohol, filtered off, and dried. The product sublimed at 226–228°, and gave a positive test (8) for an α-amino acid with "ninhydrin."

Anal. Calc'd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85.
Found: C, 67.43; H, 5.82; N, 9.95.

This product was identified as the dipeptide of *α-aminophenylacetic acid* by reason of the following behavior. A solution of the material in concentrated hydrochloric acid was heated for forty-five minutes and then evaporated to dryness by means of a stream of air. The solid, crystalline residue was recrystallized from hot, diluted alcohol, in which it is difficultly soluble, to give white crystalline plates which sublimed at 246.5–250.0°. No deviation from this temperature of sublimation occurred as a result of mixing this acid-hydrolytic product with a known sample of α-aminophenylacetic acid (9, 10, 11) recrystallized from the same solvent. A dilute hydrochloric acid solution of 0.03 g. of this hydrolytic product was treated with a slight excess of sodium nitrite and heated for forty minutes, and then was concentrated to dryness under a jet of air. The residue was extracted with ether, and the extract evaporated to yield crystalline, solid material which was recrystallized from a mixture of benzene and Skellysolve C. The final product was identified as *dl*-mandelic acid (12) by comparison with the known material.

Finally, the reactants were heated for fourteen hours in the bomb as before except that propylene glycol containing sufficient water to facilitate solution of the potassium cyanide was employed as the solvent (6). Again, the chief product isolated as IV, but a small amount of III also was detectable,

Interaction of α-(4-morpholinyl)propiophenone (I) and potassium cyanide. A solution of 5.2 g. (0.02 mole) of the hydrochloride of I in 20 cc. of water was made just basic to litmus with 5% sodium hydroxide solution. The liberated I was redissolved by addition of

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[7] Kolb (3) reported m.p. 125–126°; Collet (4) recorded m.p. 124–125°; Gabriel (5) noted m.p. 125–126°.

25 cc. of alcohol, and a solution of 1.95 g. (0.03 mole) of potassium cyanide in 5 cc. of water was then added. The mixture was placed in a glass-lined bomb and was heated at 110° for fourteen hours. On opening the cold bomb, the odor of ammonia could be recognized. The reaction mixture was diluted with water, evaporated to smaller volume by means of a stream of air, and extracted twice with ether to remove some oil which had separated. The ether extracts were combined and dried over calcium chloride before being saturated with anhydrous hydrogen chloride; thus was obtained 4 g. of the hydrochloride of I.

The ether-extracted aqueous layer was acidified with hydrochloric acid, heated, and filtered while hot to remove a small amount of amorphous material. On cooling, the filtrate yielded a white, crystalline solid which was identified as *benzoic acid.* Further concentration of the filtrate and extraction with ether gave additional benzoic acid. The final filtrate gave a positive test for *dl*-mandelic acid with McCrae's reagent (12).

Interaction of α-(4-morpholinyl)propiophenone and ammonium carbonate. A. To a solution of 3 g. of the hydrochloride of I in 100 cc. of 50% alcohol was added 12 g. of ammonium carbonate cubes, and the mixture was warmed at 58–60° for one hundred sixty-four hours. The mixture was cooled to 25° and evaporated under a stream of air, causing separation of both an oil and a solid material. The latter was removed by filtration, washed with ether, dissolved in hot alcohol, the solution treated with Norit, filtered, diluted with water, and cooled to produce white needles which melted at 222.5–223.5° (corr.). This material (V) was sparingly soluble in hot benzene, from which it crystallized in small plates; the yield of purified material was 0.2 g. V was identified as *2,4-dimethyl-5-phenylimidazole.*

Anal. Calc'd for $C_{11}H_{12}N_2$: C, 76.67; H, 7.02; N, 16.26.

Found: 76.72; H, 7.05; N, 16.13.

From the washings of the crude V, and ether extraction of the reaction mixture filtrate, there was obtained 1.4 g. of unreacted I (as the hydrochloride).

B. In another experiment, 20 g. of ammonium carbonate cubes was added to a solution of 5 g. of α-(4-morpholinyl)propiophenone hydrochloride in 100 cc. of 50% alcohol. After evolution of carbon dioxide had subsided, the mixture was placed in the glass-lined bomb and heated at 112–115° for forty-eight hours. Cooled to room temperature, the mixture was evaporated to half-volume under a stream of air and then filtered to obtain solid material contaminated with adhering oil. This material was washed with hydrochloric acid before being recrystallized from hot alcohol to yield white needles which melted at 127°. The product was identified as 2,5-dimethyl-3,6-diphenylpyrazine (IV) by comparison with a known sample.

The alcoholic mother liquor from recrystallization of IV was evaporated to dryness and the residue extracted with hot Skellysolve C to separate from a small amount of violet-colored, insoluble material. The solvent was removed by evaporation and the solute was purified by solution in hydrochloric acid, treatment of this solution with Norit, filtration, and precipitation by addition of excess sodium hydroxide solution. The tan-colored product was filtered off, and separated into two portions by fractional crystallization from 50% alcohol; the less soluble portion proved to be additional IV, the more soluble fraction, purified by recrystallization from diluted alcohol, was obtained as white plates, melting at 102°, and weighed 0.04 g. This product (VI) did not dissolve either in water or in dilute solutions of acid or base; it did dissolve in concentrated hydrochloric acid with formation of a yellow color which was discharged by dilution of the colored solution with water. In all probability this material is *2,6-dimethyl-3,5-diphenylpyrazine.*

Anal. Calc'd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76.

Found: C, 82.94; H, 6.21; N, 10.88.

Preparation of 2,5-dimethyl-3,6-diphenylpyrazine (IV). This compound was prepared according to a procedure analogous to that of Kolb[8] (3), but using the reactants employed

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[8] Kolb (3) synthesized IV by interaction of α-bromo-α-phenylacetone and alcoholic ammonia; the reaction products obtained by Kolb included three other bases, namely, C_4H_9NO, m.p. 89–90°; $C_{18}H_{18}N_2$, m.p. 102°; $C_{32}H_{26}N_6$, m.p. 225°.

by Collet[9] (4). A solution of 40 g. of α-bromopropiophenone in 300 cc. of alcohol saturated with ammonia was placed in a tightly stoppered flask and allowed to stand at room temperature for eight days. The excess ammonia and solvent was removed by evaporation under a stream of air, and the residue, after being extracted twice with 40-cc. portions of water, was dissolved in hot alcohol. Upon cooling to 25° there separated 9 g. of a yellow crystalline solid; the mother liquor [A] was reserved for further investigation. The solid material was dissolved in hot, concentrated hydrochloric acid and precipitated by dilution with water, was filtered off and recrystallized from hot alcohol to yield white crystals (IV) weighing 8.4 g. and melting at 127° (corr.). A probable picrate, yellow needles of melting point 153–155°, reverted to IV when washed with water.

The alcoholic mother liquor [A] from the isolation of IV was concentrated to yield a dark brown, heterogeneous, viscous mass. This material was extracted with dilute hydrochloric acid, the residue [B] being reserved for further treatment. The acidic extract was decolorized, while hot, with Norit; on addition of an excess of sodium hydroxide solution an amorphous, orange-colored substance separated and was removed by extraction with ether. Evaporation of the solid again gave a heterogeneous residue composed of both solid and sticky, resinous material. Removal of the latter was accomplished by extracting with a small quantity of benzene. The solid residue was recrystallized from hot, diluted alcohol to yield 0.25 g. of white needles,[10] melting at 222.5–223.5°, which dissolved readily both in alcohol and in dilute hydrochloric acid, but was sparingly soluble in hot water, benzene and ether. A picrate[11] formed readily and was obtained, after one recrystallization from warm, diluted alcohol, as fine, yellow needles. Dried in a vacuum desiccator over concentrated sulfuric acid, the *picrate* upon being heated exhibited preliminary softening at 167–168°, but melted at 174.5–175.5°; upon cooling, the fused picrate resolidified and then remelted at 167–168°.

Anal. Calc'd for $C_{11}H_{12}N_2 \cdot C_6H_3N_3O_7$: C, 50.87; H, 3.77; N, 17.45.
Found: C, 50.69; H, 3.99; N, 17.51.

The residue [B], remaining after extraction with hydrochloric acid, was partially dissolved in concentrated hydrochloric acid, the solution was extracted with ether to remove an acid-insoluble, dark-colored oil, and decolorized, while hot, with Norit. Upon cooling there separated a brown-colored solid which was filtered off; the filtrate [C] was subsequently examined. The solid material, which gave a positive test for halogen, was dissolved in hot, diluted alcohol and decolorized with Norit. Concentration of the filtrate to half-volume and addition of an excess of sodium hydroxide solution caused precipitation of an amorphous solid which was removed by extraction with ether. Removal of that solvent left an amber-colored oil. The latter was dissolved in benzene; dilution with Skellysolve C caused precipitation of a halogen-free solid. Upon recrystallization from hot, diluted alcohol, white crystalline plates,[12] melting at 214–215°, were obtained; weight 0.32 g. This substance (VII) was identified as 2,5-diphenyl-4-methylimidazole (7) by comparison with an authentic sample prepared from benzamidine and α-bromopropiophenone in chloroform solution.

Anal. Calc'd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96.
Found: C, 81.92; H, 6.01; N, 11.98.

To the acidic filtrate [C] was added an excess of concentrated ammonium hydroxide solution causing formation of an orange-colored, gummy solid material. This was removed by filtration, dissolved in hot alcohol, and the solution diluted with water until a slight

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[9] Collet noted only the formation of IV from reaction between α-bromopropiophenone and alcoholic ammonia.

[10] This substance was shown to be identical with the product (V) formed by interaction of I with ammonium carbonate.

[11] The properties listed are the same as those of the base (to which the formula $C_{32}H_{36}N_6$ was assigned) which Kolb (3) noted as forming a picrate of m.p. 165–166°.

[12] Kunckel (7) reported m.p. 215°.

turbidity resulted, then Norit was added and the mixture was digested for a while before being filtered. The filtrate was evaporated to dryness under a jet of air; the solid residue was separated into two fractions by fractional crystallization from diluted alcohol. The less soluble fraction, weighing 0.3 g., proved to be additional IV; the more soluble portion, (VI)[13] comprising 0.2 g. of white crystalline plates, melted at 102° and was readily soluble in alcohol, benzene and ether, was insoluble in water or dilute hydrochloric acid, but did dissolve in concentrated hydrochloric acid to give a yellow solution whose color was discharged by dilution with water.[14]

SUMMARY

1. α-(4-Morpholinyl)propiophenone reacts at 105° with potassium cyanide and ammonium carbonate in diluted alcohol chiefly to form 2,5-dimethyl-3,6-diphenylpyrazine.

2. Interaction of α-(4-morpholinyl)propiophenone with ammonium carbonate at 60° in diluted alcohol yields 2,4-dimethyl-5-phenylimidazole, whereas at 115° the products are 2,5-dimethyl-3,6-diphenylpyrazine and 2,6-dimethyl-3,5-diphenylpyrazine.

3. Reinvestigation of the synthesis of 2,5-dimethyl-3,6-diphenylpyrazine has clarified previous findings by Kolb; when this compound is prepared by interaction of α-bromopropiophenone and ammonia in alcoholic solution, as byproducts of this reaction were identified, 2,6-dimethyl-3,5-diphenylpyrazine, 2,4-dimethyl-5-phenylimidazole, and 2,5-diphenyl-4-methylimidazole.

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[13] This substance was proved to be identical with the compound $C_{18}H_{18}N_2$ mentioned above (section B). Although the molecular formula is identical with that of IV, the melting point of a mixture of equal parts of IV with this material (VI) was found to be 85–90°, *i.e.*, a depression of about 20–40°. Hence, the structure of VI is assumed to be 2,6-dimethyl-3,5-diphenyl pyrazine.

[14] The properties here listed are the same as those of a base thought by Kolb (3) to be a dihydrodimethyldiphenylpyrazine ($C_{18}H_{18}N_2$), but they do not correspond to those of any of the possible dihydrodimethyldiphenylpyrazines as prepared by Gabriel (5). The latter considered Kolb's compound to be probably impure 2,5-dimethyl-3,6-diphenylpyrazine.