

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

Some Isomers of Amidone and Related Compounds

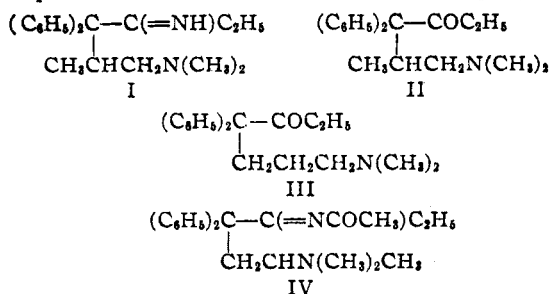
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In a recent Communication to the Editor¹ from this Laboratory, it was stated that 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile, the lower melting nitrile formed in the original Amidone synthesis,² reacts with ethylmagnesium bromide to give a ketimine (I), salts of which are readily isolated in a pure state. This ketimine hydrolyzes with difficulty to the corresponding ketone (II), which has been given the trivial name, Isoamidone II. After the ketimine had been boiled with 20% hydrochloric acid for five hours, some unreacted ketimine was isolated from the crude mixture in the form of its sesquioxalate. Its identity was confirmed by the preparation of the dipicrate.

On working up the product obtained from the reaction of ethylmagnesium bromide with the crude mixture prepared by the condensation of diphenylacetonitrile and 1-dimethylamino-2-chloropropane, another isomer of Amidone, designated as Isoamidone I, has been found in addition to Amidone and Isoamidone II ketimine. The details of this work are now described in the Experimental Part of this paper. The structure of Isoamidone I has not yet been determined, but is being studied at the present time.

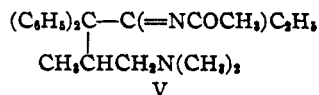
In this connection, 7-dimethylamino-4,4-diphenyl-3-heptanone (III) was prepared and characterized as the hydrochloride, picrate and methiodide. All of these salts were markedly different from the corresponding salts of Isoamidone I. Also, the ketimine of III was isolated as the picrate.

As further members of this series of compounds, the acetyl ketimine related to Amidone has been prepared as the base (IV) and hydrochloride. The acetyl ketimine (V) related to Isoamidone II was found to be an oil which was converted into the hydrochloride without purification. Also, the dipicrate of Amidone ketimine has been prepared.



(1) N. R. Easton, J. H. Gardner and J. R. Stevens, *THIS JOURNAL*, **69**, 978 (1947).

(2) Office of the Publication Board, Department of Commerce, Report PB 981, p. 96; E. M. Schultz, C. M. Robb and J. M. Sprague, *THIS JOURNAL*, **69**, 188 (1947); W. R. Brode and M. W. Hill, *ibid.*, **69**, 724 (1947).



Experimental

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone-imine (I).—To an ethereal solution of ethylmagnesium bromide prepared from 26.4 g. (1.08 moles) of magnesium turnings and 132 g. (1.21 moles) of ethyl bromide in 180 ml. of ether, there was added during a half hour, with stirring, a solution of 150 g. (0.53 mole) of 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile³ in 150 ml. of xylene. The mixture was heated on a water-bath for three hours. The mixture was then poured into a solution of 170 ml. of concentrated hydrochloric acid in 300 ml. of water. A vigorous reaction resulted, evaporating the xylene and ether. The acid solution was made alkaline with 50% sodium hydroxide. Celite 503 was added and the mixture filtered. Both the precipitate and filtrate were extracted with ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness, leaving 147 g. of the crude ketimine as an oily residue.

For the preparation of the sesquioxalate, the oil was treated with an equal weight of oxalic acid dissolved in alcohol. On cooling and scratching, the sesquioxalate crystallized. After crystallization from a mixture of alcohol and ether, it melted at 145–146°.

Anal. Calcd. for $2\text{C}_{21}\text{H}_{28}\text{N}_2 \cdot 3\text{H}_2\text{C}_2\text{O}_4$: C, 64.99; H, 7.05; N, 6.32; $\text{H}_2\text{C}_2\text{O}_4$, 30.45. Found: C, 65.15; H, 6.96; N, 6.36; $\text{H}_2\text{C}_2\text{O}_4$, 30.50.

The dihydrochloride was prepared by treating an alcoholic solution of the ketimine with the theoretical amount of 30% alcoholic hydrogen chloride. On standing, an oil separated which eventually crystallized. After crystallization from a mixture of alcohol and ether, the white crystals melted at 200–202° dec.

Anal. Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_2 \cdot 2\text{HCl}$: C, 66.13; H, 7.93; N, 7.35; Cl, 18.59. Found: C, 66.00; H, 7.75; N, 7.30; Cl, 18.43.

For the preparation of the dipicrate, the oily ketimine was dissolved in alcohol and a hot alcoholic solution of picric acid was added. The mixture was heated on the steam-bath and crystals formed. The solid material was separated and recrystallized successively from acetone, acetone containing a little picric acid and from ethyl acetate. The yellow product melted at 140–141°, and could be converted into a more stable form, m. p. 166.5–168° by crushing on a porous plate or by boiling for some time in alcohol. *Anal.* Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.65, 51.75; H, 4.54, 4.38; N, 14.41, 14.58.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II (II)] Oxalate.—A solution of 17.4 g. of the ketimine dihydrochloride in 150 ml. of 20% hydrochloric acid was refluxed for five hours, cooled and made alkaline with 50% sodium hydroxide. After cooling, it was extracted twice with ether. The ether solution was concentrated to about 50 ml. and a solution of 17.5 g. of oxalic acid in 75 ml. of alcohol was added. On cooling and scratching, crystals were deposited. After crystallization from a mixture of acetone and alcohol, the yield was 9.7 g. (47%), m. p. 163–164°.

Anal. Calcd. for $2\text{C}_{21}\text{H}_{27}\text{ON} \cdot 3\text{H}_2\text{C}_2\text{O}_4$: C, 64.86; H, 6.76; N, 3.15; $\text{H}_2\text{C}_2\text{O}_4$, 30.41; neut. equiv., 148. Found: C, 65.2; H, 6.66; N, 3.43, 3.39; $\text{H}_2\text{C}_2\text{O}_4$, 30.40; neut. equiv., 149.

On diluting the original mother liquor with ether to complete precipitation, an oil was deposited which slowly

crystallized on standing in the refrigerator. The liquid was decanted and the residue recrystallized twice from a mixture of acetone and alcohol, giving white crystals, m. p. 145–146°. A mixed melting point with Isoamidone II ketimine sesquioxalate showed no depression. For confirmation, the base from 0.5 g. of the oxalate was dissolved in 5 ml. of alcohol and treated with a solution of 0.5 g. of picric acid in 8 ml. of alcohol. The picrate came down as an oil. The alcoholic mother liquor was decanted and the oil was dissolved in about 75 ml. of hot alcohol. On cooling, the picrate formed yellow crystals, m. p. 166–167°, mixed with Isoamidone II ketimine dipicrate, m. p. 167–169°.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II Base (II)].—An aqueous solution of 7.8 g. of Isoamidone II oxalate was made alkaline with sodium hydroxide. The base was extracted with ether and the ether extract was dried over potassium carbonate. The ether was distilled. The residue was dried by heating in a water aspirator vacuum on a steam-bath and distilled in vacuum. The yield was 3.9 g. (72%) of a clear, slightly yellow, very viscous liquid, b. p. 215° under 12 mm.

Anal. Calcd. for $C_{21}H_{27}ON$: C, 81.55; H, 8.74; N, 4.53. Found: C, 81.50; H, 8.90; N, 4.54, 4.52.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone [Isoamidone II (II)] Hydrochloride, Picrate and Methiodide.—For the preparation of the hydrochloride, 16 g. of the oxalate was converted to the base as above. The crude base was treated with 8 ml. of 20% hydrochloric acid in an evaporating dish and the mixture was evaporated to dryness on a steam-bath, and finally dried at 70° in a vacuum oven. The yield of crude product was 12.5 g., m. p. 187–188°, after softening at 139°. After crystallization from isopropyl alcohol, there were obtained 5.7 g. of white crystals, m. p. 145–149°, rising to m. p. 190–193° after drying in a vacuum at 100°. Working up the mother liquors gave an additional 4.3 g. of the same m. p. after drying. The total yield was 10.0 g. (80%).

Anal. Calcd. for $C_{21}H_{27}ON \cdot HCl$: C, 72.92; H, 8.16; N, 4.05; Cl, 10.25. Found: C, 72.90; H, 8.13; N, 4.02, 4.01; Cl, 10.20.

The picrate was prepared by treating a solution of 0.4 g. of the base in 2 ml. of alcohol with a solution of 0.6 g. of picric acid in 5 ml. of hot alcohol. The solution was cooled and the yellow crystals were filtered out and after recrystallization from alcohol, the yield was 0.45 g. (64.5%), m. p. 149–150°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 59.95; H, 5.54; N, 10.55, 10.52.

For the preparation of the methiodide, the base from 2 g. of the oxalate was dissolved in ether. The ether solution was dried over magnesium sulfate, filtered and an excess of methyl iodide was added. On standing crystals, m. p. 263–264°, unchanged by recrystallization from methanol, separated.

Anal. Calcd. for $C_{22}H_{29}ONI$: C, 58.54; H, 6.70; N, 3.10; I, 28.11. Found: C, 58.45; H, 6.78; N, 3.06; I, 28.25, 28.35.

Isolation of Isoamidone I.—Diphenylacetone nitrile (213.5 g.) was condensed with 133 g. of 1-dimethylamino-2-chloropropane by the procedure described in the Report PB 981.³ The crude mixture of nitriles was treated with ethylmagnesium bromide and the resulting complex decomposed as described in the Report. The three layers which formed were separated. The middle layer was made alkaline with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and concentrated to a thick oil. The oil was dissolved in absolute alcohol and the calculated amount of absolute alcoholic hydrogen chloride was added. Amidone hydrochloride crystallized and was recrystallized from absolute alcohol. The yield was 54 g., m. p. 229–231°.

The mother liquor was concentrated, neutralized with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and

evaporated to dryness, leaving an oil. An equal weight of oxalic acid dissolved in alcohol was added to the oil. On adding anhydrous ether and scratching, 13 g. of Isoamidone I oxalate, m. p. 158–160°, crystallized. A sample for analysis was recrystallized from acetone, with no change in melting point.

Anal. Calcd. for $C_{21}H_{27}ON \cdot H_2C_2O_4$: C, 69.15; H, 7.32. Found: C, 69.20; H, 7.06.

The base was liberated by the addition of sodium hydroxide to an aqueous solution of the oxalate and was extracted with ether. The ether solution was washed with water and dilute ammonium hydroxide and dried over magnesium sulfate. The ether was distilled and the residue dried by heating under reduced pressure.

Anal. Calcd. for $C_{21}H_{27}ON$: C, 81.50; H, 8.80; N, 4.53. Found: C, 81.34; H, 8.84; N, 4.76, 4.73.

A sample, when distilled under 3 mm. pressure, boiled at 164–167°.

The hydrochloride was prepared by the addition of alcoholic hydrogen chloride and anhydrous ether to the base. After crystallization from acetone, it melted at 172–173°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot HCl$: C, 72.92; H, 8.16; N, 4.05; Cl, 10.25. Found: C, 73.05; H, 8.21; N, 4.25, 4.22; Cl, 10.25.

The methiodide was prepared by adding methyl iodide to an ethereal solution of the crude base. After crystallization from a mixture of acetone and di-isopropyl ether, it melted at 195–196°.

Anal. Calcd. for $C_{22}H_{29}ONI$: C, 58.53; H, 6.70; I, 28.11. Found: C, 58.65; H, 6.85; I, 28.40, 28.50.

For the preparation of the picrate, a sample of the base liberated from the hydrochloride was dissolved in alcohol and treated with a solution of an equal weight of picric acid in alcohol. After crystallization twice from alcohol and drying in vacuum at 77°, it melted at 131–133°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 60.05; H, 5.54; N, 10.61, 10.62.

For the isolation of Isoamidone II ketimine, the bottom layer from the decomposition of the original complex was neutralized with 50% sodium hydroxide and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to dryness. The residue was dissolved in alcohol and absolute alcoholic hydrogen chloride was added. After adding anhydrous ether and scratching, 12 g. of crystals, m. p. 195–200°, separated. A sample was recrystallized from absolute alcohol and then melted at 200–202°. A mixture with an authentic sample of Isoamidone II ketimine dihydrochloride melted at 199–201°.

To determine whether Isoamidone I might be a molecular compound between Amidone and Isoamidone II, the melting point ranges of several mixtures of the hydrochlorides of the last two compounds were determined. Each mixture melted over a wide range with an upper limit of 190° or higher and the melting range of no mixture approached that of Isoamidone I hydrochloride. The data are shown in Table I.

TABLE I

Hydrochlorides of Amidone, %	Isoamidone II, %	Softened, °C.	Completely melted, °C.
76	24	175	218
55	45	176	211
28	72	145	190

A mixture made up of approximately equal amounts of the hydrochlorides of Amidone and Isoamidone II was dissolved in alcohol and precipitated by the addition of ether. The resulting granular precipitate softened at 157° and was completely melted at 200°.

5-Dimethylamino-2,2-diphenylpentanenitrile.—To a well-stirred suspension of 9 g. of sodamide in 50 ml. of dry benzene, warmed to 45–50°, there was added, during a fifteen-minute period, 39 g. of diphenylacetone nitrile. The

temperature of the reaction mixture was maintained at 40–45° for one and one-half hours. The mixture was cooled to 20–25° and 25 g. of 3-dimethylaminopropyl chloride was added during thirty minutes. The mixture was refluxed for five hours. After standing overnight, the mixture was poured into water. The water layer was separated and discarded. The benzene layer was extracted with 20% hydrochloric acid. The acid layer was neutralized with 10% sodium hydroxide and extracted with ethyl ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness. The product was recrystallized from petroleum ether and from Skellysolve C. The yield of white crystals melting at 64–65° was 19.4 g.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.95, 81.90; H, 7.82, 7.98; N, 10.09, 10.02.

7-Dimethylamino-4,4-diphenyl-3-heptanone (III) Hydrochloride, Picrate and Methiodide.—A solution of 25.4 g. of 5-dimethylamino-2,2-diphenylpentanenitrile in 20 ml. of xylene was added to a Grignard reagent prepared from 4.4 g. of magnesium and 22 g. of ethyl bromide in 20 ml. of ether. The reaction mixture was heated on a steam-bath for five and one-half hours. After standing overnight, it was poured into a solution of 40 ml. of concentrated hydrochloric acid in 100 ml. of water. Two layers were formed. The water layer was separated, made alkaline with 10% sodium hydroxide and extracted with ether. The ether solution was dried over magnesium sulfate, filtered and evaporated to dryness, leaving 28 g. of an oil.

A small portion of the oil was converted into a picrate, m. p. 181–182°, in the usual way. Analysis showed it to be the dipicrate of the ketimine.

Anal. Calcd. for $C_{21}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.50; H, 4.59; N, 14.50, 14.51.

The remaining oil was boiled with concd. hydrochloric acid for five hours. The mixture was cooled, made alkaline with 10% sodium hydroxide and extracted with ether. After being dried over magnesium sulfate, the ether solution was treated with dry hydrogen chloride. The oil which separated gradually crystallized. The solid was dissolved in ethyl acetate, treated with Nuchar C, filtered and the resulting solution was cooled. The white crystals which separated melted at 139–140°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot HCl$: C, 72.92; H, 8.16; N, 4.05. Found: C, 73.00; H, 8.30; N, 4.06.

The picrate was prepared by treating the base liberated from the hydrochloride with picric acid in alcohol. After crystallizing from the same solvent, it melted at 118–119°.

Anal. Calcd. for $C_{21}H_{27}ON \cdot C_6H_3O_7N_3$: C, 60.21; H, 5.62; N, 10.40. Found: C, 60.30; H, 5.85; N, 10.32.

The methiodide was prepared by treating the base with methyl iodide in ether. After crystallizing from methanol, it melted at 250–252°.

Anal. Calcd. for $C_{22}H_{30}ONI$: C, 58.54; H, 6.70; N, 3.10; I, 28.11. Found: C, 58.25; H, 6.98; N, 3.16; I, 28.55.

6-Dimethylamino-4,4-diphenyl-3-heptanone-acetylimine (IV).—4-Dimethylamino-2,2-diphenylpentanenitrile was treated with ethylmagnesium bromide according to the procedure for the preparation of Amidone by the original method.² The resulting mixture was poured into acetic anhydride with cooling in an ice-bath. Ethyl alcohol was

added and most of the solid precipitate dissolved. The mixture was concentrated under reduced pressure and the residue dissolved in water. After making alkaline with sodium hydroxide, the base was extracted with ether. The ether solution was dried over magnesium sulfate and evaporated to dryness. The residue crystallized on standing and was recrystallized from Skellysolve C, m. p. 130–131°.

Anal. Calcd. for $C_{23}H_{30}ON_2$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.90; H, 8.70; N, 8.08.

The hydrochloride was prepared by passing dry hydrogen chloride into a solution of the base in di-isopropyl ether. After recrystallizing from acetone, it melted at 219–221°.

Anal. Calcd. for $C_{23}H_{30}ON_2 \cdot HCl$: C, 71.38; H, 8.08; N, 7.24; Cl, 9.16. Found: C, 71.30; H, 8.17; N, 7.23; Cl, 9.14.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone-acetylimine (V) Hydrochloride.—A mixture of 25 g. of the ketimine and 50 g. of acetic anhydride was heated on the steam-bath for about three hours, and then concentrated under reduced pressure. The residue was dissolved in water and the solution made alkaline with sodium hydroxide. The base was extracted with ether, the ether solution dried over magnesium sulfate and evaporated to dryness. On attempting to prepare the oxalate in the usual way, an oil which did not crystallize was formed. The base was regenerated and converted into the hydrochloride by adding an alcoholic solution of hydrogen chloride and then ether. The hydrochloride crystallized on scratching; m. p. 213–215°.

Anal. Calcd. for $C_{23}H_{30}ON \cdot HCl$: C, 71.38; H, 8.08; N, 7.24; Cl, 9.16. Found: C, 71.45; H, 8.12; N, 7.23; Cl, 9.15.

6-Dimethylamino-4,4-diphenyl-3-heptanoneimine (Amidone Ketimine) Dipicrate.—Ethylmagnesium bromide was brought into reaction with 4-dimethylamino-2,2-diphenylpentanenitrile as in the original preparation of Amidone.² On completion of the reaction, the reaction mixture was poured into a mixture of ice and 30% acetic acid. After neutralization with 10% sodium hydroxide, the mixture was extracted with ether. The ether solution was dried over magnesium sulfate, filtered and concentrated. A portion of the residue was dissolved in alcohol and treated with an alcoholic solution of picric acid. The solid which precipitated was recrystallized from a mixture of ethyl acetate and acetone. The yellow product melted at 182–184°.

Anal. Calcd. for $C_{21}H_{28}N_2 \cdot 2C_6H_3O_7N_3$: C, 51.69; H, 4.47; N, 14.62. Found: C, 51.60; H, 4.28; N, 14.68, 14.65.

Acknowledgment.—We are indebted to Dr. V. B. Fish of this Laboratory for the analyses reported in this paper.

Summary

1. Three isomers of Amidone have been described.
2. Four ketimine derivatives related to Amidone have been prepared.

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