[CONTRIBUTION FROM THE SCHENLEY LABORATORIES]

The Mannich Reaction on α,α-Diphenylacetone

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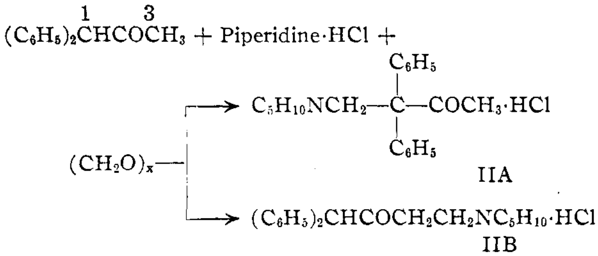
The reaction of α,α-diphenylacetone with piperidine hydrochloride and paraformaldehyde yields 1,1-diphenyl-4-(N-piperidyl)-butanone-2 hydrochloride (IIB). The structure was confirmed by reduction to 1,1-diphenyl-4-(N-piperidyl)-butanol-2 hydrochloride, dehydration of the carbinol to 1,1-diphenyl-4-(N-piperidyl)-butene-1 hydrochloride and comparison of this butene with a sample prepared by an unequivocal method.

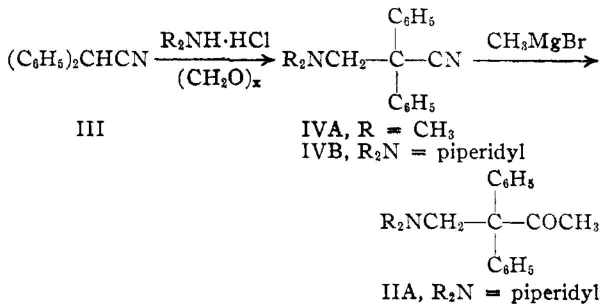
In the course of work directed toward the synthesis of pharmacodynamic compounds we investigated the reaction of α,α-diphenylacetone (I) with secondary amines and formaldehyde.[1a] The possibility that two products (IIA and IIB) derived from condensation at carbon atoms 1 or 3 could be formed was anticipated. In all the reactions only one product was obtained. After this work was well underway a report by Jilek and Protiva[1b] appeared describing the same reaction and favoring structure IIA. A second communication[2] by these same workers cast doubts on the correctness of structure IIA but no definitive evidence was presented for either IIA or IIB.



$$(C_6H_5)_2\overset{1}{C}H\overset{3}{C}OCH_3 + \text{Piperidine}\cdot HCl + (CH_2O)_x \longrightarrow C_5H_{10}NCH_2-\underset{C_6H_5}{\overset{C_6H_5}{C}}-COCH_3\cdot HCl\ (\text{IIA});\quad (C_6H_5)_2CHCOCH_2CH_2NC_5H_{10}\cdot HCl\ (\text{IIB})$$

We favored structure IIB as the correct formulation for two reasons. The Mannich base gave a negative iodoform reaction when the modified procedure of Adachi[3] was applied whereas α,α-diphenylacetone gave a positive test. On the basis of the positive test obtained with I it is to be expected that IIA should also give a positive reaction.

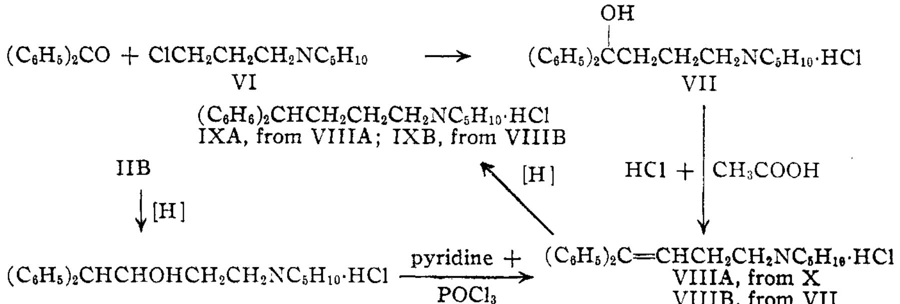
Bockmühl and Ehrhart[4] described the successful Mannich reaction of diphenylacetonitrile with dimethylamine and formaldehyde to give IVA. We attempted to prepare IVB as a possible intermediate in an unequivocal synthesis of IIA. When we employed the Mannich reaction conditions which proceeded so smoothly with α,α-diphenylacetone to diphenylacetonitrile and used piperidine hydrochloride in place of the dimethylamine hydrochloride as described by Bockmühl no reaction occurred. The piperidine hydrochloride was recovered in 95% yield. This lack of reaction indicates the existence of a pronounced steric effect in diphenylacetonitrile and, analogously, the existence of a similar steric effect at carbon atom 1 in α,α-diphenylacetone. This steric effect is well illustrated by the use of Fisher–Taylor–Hirschfelder models and could overbalance the more favorable electronic distribution which exists at carbon atom 1 for the Mannich reaction. The above approach to the synthesis of IIA was abandoned in favor of the rigorous structure proof outlined in the following flow sheet.



$$\underset{\text{III}}{(C_6H_5)_2CHCN} \xrightarrow[(CH_2O)_x]{R_2NH\cdot HCl} R_2NCH_2-\underset{C_6H_5}{\overset{C_6H_5}{C}}-CN \xrightarrow{CH_3MgBr} R_2NCH_2-\underset{C_6H_5}{\overset{C_6H_5}{C}}-COCH_3$$

IVA, $R = CH_3$
IVB, R_2N = piperidyl
IIA, R_2N = piperidyl

FLOW SHEET



$$\underset{\text{VI}}{(C_6H_5)_2CO + ClCH_2CH_2CH_2NC_5H_{10}} \longrightarrow \underset{\text{VII}}{(C_6H_5)_2\overset{OH}{C}CH_2CH_2CH_2NC_5H_{10}\cdot HCl}$$

$$\text{VII} \xrightarrow{HCl\ +\ CH_3COOH} \underset{\text{VIIIA, from X; VIIIB, from VII}}{(C_6H_5)_2C{=}CHCH_2CH_2NC_5H_{10}\cdot HCl} \xrightarrow{[H]} \underset{\text{IXA, from VIIIA; IXB, from VIIIB}}{(C_6H_5)_2CHCH_2CH_2CH_2NC_5H_{10}\cdot HCl}$$

$$\text{IIB} \xrightarrow{[H]} \underset{\text{X}}{(C_6H_5)_2CHCHOHCH_2CH_2NC_5H_{10}\cdot HCl} \xrightarrow[POCl_3]{\text{pyridine} +} \text{VIIIA}$$

The elegant procedure for the condensation of γ-chloroalkylamines with ketones described by Miescher and Marxer[5a,b] was used to prepare VII. This method makes use of the activated Grignard reagent of the γ-chloroalkylamines. A refluxing mixture of glacial acetic acid and hydrochloric acid employed by Adamson[6] to dehydrate similar alcohols afforded VIIIB in 60% yield. Catalytic hydrogenation with Adams catalyst yielded IXB

(1a) NOTE ADDED IN PROOF:—Subsequent to the admission of this material to the *Journal* an article by Wilson and Kyi in the *J. Chem. Soc.*, 1321 (1952), appeared in which the same conclusion concerning the nature of the Mannich base was reached. These authors relied on degradative evidence to determine the structure of IIB.

(1b) J. O. Jilek and M. Protiva, *Chem. Listy*, **44**, 49 (1950). See also *C. A.*, **45**, 7987^d (1951).

(2) M. Protiva and J. Jilek, *Chem. Listy*, **45**, 207 (1951). The authors are grateful to Drs. Protiva and Jilek for a reprint of this article prior to its appearance in *Chemical Abstracts*.

(3) J. Adachi, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **71**, 566 (1950), or *C. A.*, **45**, 6541 (1951).

(4) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 52 (1949).

(5) K. Miescher and A. Marxer, U. S. Patent 2,411,664 (November 26, 1946); (b) A. Marxer, *Helv. Chim. Acta*, **24**, 209 (1941).

(6) D. W. Adamson, *J. Chem. Soc.*, 144 (1949).

synthesized earlier by Bockmühl and Ehrhart[7] by the sodamide condensation of VI with diphenylmethane.

The Mannich base, IIB, was hydrogenated to the secondary alcohol X. This carbinol resisted standard dehydration techniques such as refluxing acetic anhydride, 48% hydrobromic acid, mixtures of acetic and hydrochloric acid or 60% sulfuric acid. X could be dehydrated in 67% yield using pyridine and phosphorus oxychloride as described by Hamlet, *et al.*[8] This unsaturated product VIIIA was identical in every respect with VIIIB prepared by an unequivocal method. Reduction of the butene VIIIA afforded IXA—further proof that the original Mannich base is correctly represented by IIB.

The ultraviolet absorption spectra of VIIIA and VIIIB were determined to 4000 Å. and were identical within experimental error.

A direct proof of the structure of IIB could have been accomplished by the reduction of the keto group to the methylene group and comparison of the reduced product with IX. When we attempted to carry out a Wolff–Kishner reduction using the modification of Huang-Minlon,[9] decomposition of the base occurred as evidenced by the strong odor of piperidine. It is noteworthy to point out that Jilek and Protiva[2] tried the same reduction and obtained similar results. These investigators isolated diphenylmethane from the reaction mixture, characterizing it as the 4,4′-dinitro derivative.

Acknowledgment.—The authors are grateful to Drs. K. Ladenburg and B. Puetzer for continued encouragement in this work and to Mr. Gabor B. Levy for the determination of the ultraviolet spectra.

Experimental[10,11]

1,1-Diphenyl-4-(N-piperidyl)-butanone-2 Hydrochloride (IIB).—Into a 100-ml. flask equipped for refluxing were charged 4.0 g. (0.019 mole) of α,α-diphenylacetone,[12] 2.65 g. (0.022 mole) of piperidine hydrochloride, 1.3 g. (0.04 mole) of paraformaldehyde and 13 ml. of *n*-amyl alcohol. This mixture was heated to reflux in ten minutes and the resulting amber solution refluxed two hours longer. The hot solution was poured into a 250-ml. beaker and set almost immediately to a semi-solid cake. This cake was cooled to room temperature, mixed with 20 ml. of acetone and filtered. The white solid was washed with 100 ml. of acetone and dried at 60°. The weight of material, m.p. 200–203°, was 4.3 g. (66%). A recrystallized sample melted at 204–205°. Jilek and Protiva reported the m.p. as 204–205°.

1,1-Diphenyl-4-(N-piperidyl)-butanol-2 Hydrochloride (X).—Into a pressure bottle were charged 3.5 g. (0.01 mole) of IIB, 50 ml. of methanol and 0.2 g. of PtO_2. This mixture was hydrogenated in a Parr apparatus at 15 lb. pressure for two hours. The solution was filtered from the catalyst and concentrated to dryness. The residual oil was triturated with methyl ethyl ketone to yield 3.3 g. of solid melting at 155–158°. After three recrystallizations from methyl ethyl ketone a sample was sent for analysis; m.p. 182–183°.

Anal. Calcd. for $C_{21}H_{28}ONCl$: C, 72.98; H, 8.10; Cl, 10.27. Found: C, 73.19; H, 8.12; Cl, 10.39.

1,1-Diphenyl-4-(N-piperidyl)-butene-1 Hydrochloride (VIIIA).—A modification of the method of Hamlet[8] was followed. A solution of 4.5 g. (0.013 mole) of X in 10 ml. of dry pyridine was prepared in a 100-ml. flask protected by a $CaCl_2$ tube. A previously prepared cold solution of 10 ml. of $POCl_3$ in 25 ml. of dry pyridine was added so that the temperature did not exceed 30°. The mixture was maintained at 30° for one-quarter hour and heated on a steam-bath for three-quarters of an hour. After cooling, the solution was added to 300 g. of ice, the resulting solution made distinctly alkaline with 5 *N* NaOH and extracted with three 250-ml. portions of ether. The ether extracts were combined, dried over $MgSO_4$ and the solvents were removed *in vacuo* using a steam-bath to heat the flask. The residual oil was redissolved in ether and treated with dry hydrogen chloride. The flocculent white precipitate was collected and recrystallized once from ethyl acetate and a trace of methanol; yield 2.7 g. (63%), m.p. 173–175°. A sample recrystallized three times more melted at 178–179°.

Anal. Calcd. for $C_{21}H_{26}NCl$: C, 76.94; H, 7.94; Cl, 10.84. Found: C, 77.06; H, 7.83; Cl, 10.73.

1,1-Diphenyl-4-(N-piperidyl)-butane Hydrochloride (IXA).—A mixture of 1.3 g. (0.0038 mole) of VIIIA, 50 ml. of methanol and 0.1 g. of PtO_2 was hydrogenated in a Parr apparatus for two hours. After removing the catalyst by filtration the filtrate was concentrated to 10 ml. and diluted with 500 ml. of isopropyl ether. The turbid solution slowly crystallized and 1.1 g. (84%) of fine needles, m.p. 168–170°, was obtained. A sample recrystallized twice more from isopropyl alcohol–isopropyl ether melted at 171–172° (lit.[7] 172°).

Anal. Calcd. for $C_{21}H_{28}NCl$: C, 76.48; H, 8.50; Cl, 10.77. Found: C, 76.34; H, 8.36; Cl, 10.54.

IXB was prepared in the same manner. A mixed melting point of IXA and IXB showed no depression; m.p. 170–172°.

1,1-Diphenyl-1-hydroxy-4-(N-piperidyl)-butane Hydrochloride (VII).—This material was prepared as described in example 1 (U. S. Patent 2,411,664), substituting N-γ-chloropropylpiperidine[13] for N-γ-chloropropyldiethylamine. Following the procedure we obtained 20.0 g. of VII (57%), m.p. 205–207° (lit.[5b] 212–214°).

1,1-Diphenyl-4-(N-piperidyl)-butene-1 Hydrochloride (VIIIB).—A solution of 2.5 g. (0.0077 mole) of VII, 5 ml. of concd. hydrochloric acid and 15 ml. of glacial acetic acid was refluxed gently for 2.5 hours. The solution was cooled, poured into a beaker, diluted with 50 ml. of water and covered with 100 ml. of ether. The aqueous layer was made alkaline with solid sodium carbonate and the two layer system transferred to a separatory funnel. The ether layer was separated and the aqueous layer extracted with 200 ml. of ether. The ether extracts were dried over $MgSO_4$ and treated with dry hydrogen chloride. The yield of white solid, m.p. 175–176°, was 1.6 g. (69%). A sample recrystallized from ethyl acetate–methanol melted at 176–177°.

Anal. Calcd. for $C_{21}H_{26}NCl$: C, 76.94; H, 7.94; Cl, 10.84. Found: C, 76.94; H, 8.11; Cl, 10.77.

When a sample was mixed with a sample of VIIIA no depression in melting point occurred; m.p. 176–177°.

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[7] M. Bockmühl and G. Ehrhart, U. S. Patent 2,446,522 (August 10, 1948).

[8] J. C. Hamlet, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 2652 (1951).

[9] Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

[10] All melting points are uncorrected.

[11] The microanalyses were carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

[12] E. M. Schultz and S. Mickey, *Org. Syntheses*, **29**, 39 (1949).

[13] The N-γ-chloropropylpiperidine was prepared as described by Marxer[5b] from piperidine and trimethylene chlorobromide.