[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

SOME REACTIONS OF AMIDONE

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This project was undertaken in order to study a number of transformations of the amidone (6-dimethylamino-4,4-diphenyl-3-heptanone) (1, 2) molecule (V) and to observe the pharmacological changes induced by such transformations.

The carbonyl group of V was found to be relatively unreactive. It did not give a semicarbazone under the usual conditions and resisted reduction with aluminum isopropoxide or sodium amalgam. It was unaffected when subjected to hydrogenation with Raney nickel at room temperature and atmospheric pressure. With platinum oxide, however, the corresponding carbinol (II) was formed in a yield of 80%; only one of the two possible diastereoisomers was isolated. Acetylation of II with acetic anhydride and pyridine gave a 40% yield of the O-acetyl derivative (I-a). By the method of Houben (3) (acid anhydride, ethylmagnesium bromide) I was obtained in yields of 80–90%.

By the action of thionyl chloride II was converted, under mild conditions, to a mixture of 3-chloro-6-dimethylamino-4,4-diphenylheptane (IV) (40% yield) and 6-dimethylamino-4,4-diphenylheptene-2 (III) (20% yield). When the reaction was carried out in boiling benzene, the yield of IV was about 10% and that of III 30–40%. Results similar to the latter were obtained with II and phosphorus pentachloride in chloroform. Finally III was formed in yields of 30–40% on treatment of II with phosphorus pentoxide in boiling toluene, and in the reaction of II or IV with hydriodic acid and phosphorus in boiling acetic acid. Efforts to hydrogenate III and IV under a wide variety of conditions gave erratic results. Hydrogen absorption either did not proceed at all, or else showed no tendency to cease at any definite molar stage. No crystalline, homogeneous reduction products could be isolated from the resulting mixtures.

Amidone was not attacked in the Clemmensen reduction. When it was subjected to the Wolff-Kishner reaction as modified by Huang-Minlon (4), a product was obtained which, on the basis of carbon-hydrogen analysis of three of its salts,[1] appeared to be isomeric with V. However, on degradation of this product it became obvious that it was 3-dimethylamino-1,1-diphenylbutane (VI), formed by alkaline cleavage of the ethyl keto group. Omission of the hydrazine did not alter the course of the reaction, while omission of both the hydrazine and the alkali led to extensive decomposition of V. Essentially no reaction took place when V and concentrated hydrochloric acid were heated together at 200°.

Hofmann degradation of the methiodide of VI (which was formed also by alkali treatment of the methiodide of V) and hydrogenation of the resulting olefin (X) gave 1,1-diphenylbutane (IX). This hydrocarbon was obtained in low

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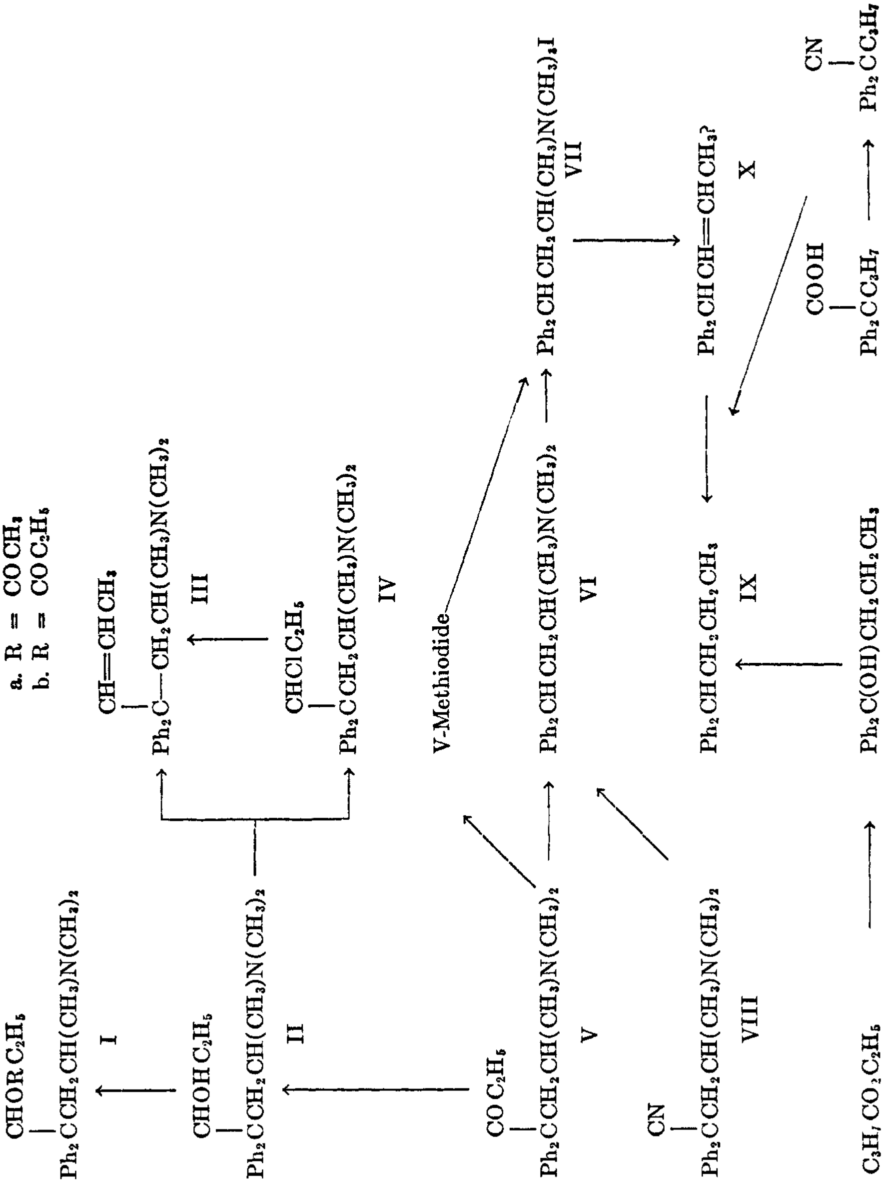
[1] Hydrochloride. Calc'd for $C_{21}H_{28}ClNO$: C, 72.9; H, 8.2. Found: C, 73.2; H, 8.2. Picrate. Calc'd for $C_{27}H_{30}N_4O_8$: C, 60.2; H, 5.6. Found: C, 60.3; H, 5.4. Perchlorate. Calc'd for $C_{21}H_{28}ClNO_5$: C, 61.5; H, 6.9. Found: C, 61.3; H, 6.8.


a. R = COCH₃
b. R = COC₂H₅
Ph₂C(CHOR C₂H₅)CH₂CH(CH₃)N(CH₃)₂
I
Ph₂C(CHOH C₂H₅)CH₂CH(CH₃)N(CH₃)₂
II
Ph₂C(CH=CHCH₃)—CH₂CH(CH₃)N(CH₃)₂
III
Ph₂C(CHCl C₂H₅)CH₂CH(CH₃)N(CH₃)₂
IV
Ph₂C(CO C₂H₅)CH₂CH(CH₃)N(CH₃)₂
V
V-Methiodide
Ph₂CHCH₂CH(CH₃)N(CH₃)₂
VI
Ph₂CHCH₂CH(CH₃)N(CH₃)₃I
VII
Ph₂C(CN)CH₂CH(CH₃)N(CH₃)₂
VIII
Ph₂CHCH₂CH₂CH₃
IX
Ph₂CHCH=CHCH₃?
X
C₃H₇CO₂C₂H₅
Ph₂C(OH)CH₂CH₂CH₃
Ph₂C(COOH)C₃H₇
Ph₂C(CN)C₃H₇

yield, along with α,α-diphenylvaleric acid by alkali treatment of α,α-diphenylvaleronitrile, and was synthesized in an over-all yield of 50% from ethyl butyrate *via* 1,1-diphenyl-1-butanol. The latter in acetic acid[2] containing traces of perchloric acid was hydrogenated to IX with palladium-charcoal or palladium-barium sulfate catalyst. The 1,1-diphenylbutane was characterized through its solid dinitro derivative. The cleavage product VI could also be obtained in good yield by the action of alkali on 4-dimethylamino-2,2-diphenylpentanenitrile. No intermediate acid was isolated in this instance.

Conversion of amidone to the corresponding carbinol (II) results in a marked reduction of morphine-like characteristics including analgesic effect. Activity is restored practically to that of amidone by acetylation of the hydroxyl group of II and to a lesser extent by propionylation. Replacement of the hydroxyl group by chlorine gives a nearly inactive compound (IV). The olefinic compound III approximates II in activity, while the scission product VI is inactive (Nathan B. Eddy) (5).

Acknowledgment. Microanalyses are from the Institute analytical service laboratory under the direction of C. A. Kinser.

EXPERIMENTAL[3]

6-Dimethylamino-4,4-diphenyl-3-heptanol (II). A mixture of 10 g. of V hydrochloride, 0.4 g. of platinum oxide, and 50 cc. of methanol absorbed one mole of hydrogen during twelve to twenty-four hours. To the filtered solution was added 7 cc. of concentrated ammonium hydroxide and 15 cc. of water, with warming. Upon gradual cooling, finally in ice, 7.3 g. (80%) of II, m.p. 100–101° separated; prisms from aqueous methanol, m.p. 100–100.5°. V base could be hydrogenated with equal facility.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.9; H, 9.4.
Found: C, 81.1; H, 9.4.

The hydrochloride, isolated directly from the reduction mixture or prepared from the base with alcoholic hydrogen chloride, crystallized from methanol-ether in prisms of m.p. 190–193° and 200–203°.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.5; H, 8.7.
Found: C, 72.6; H, 8.6.

3-Acetoxy-6-dimethylamino-4,4-diphenylheptane (I-a) hydrochloride. To a stirred, ice-cooled solution of 1.5 g. of II in 20 cc. of dry ether was added 10 cc. of 1 *M* ethylmagnesium bromide, then 1.3 cc. of acetic anhydride in 20 cc. of dry ether. The mixture was refluxed for one-half hour, shaken overnight, and poured into ice-cold, dilute alkali. The ether was dried and acidified with 15% alcoholic hydrogen chloride to give 1.7 g. (90%) of product melting at 207–209°; prisms from methanol-ether.

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.8; H, 8.3.
Found: C, 70.5; H, 8.3.

6-Dimethylamino-4,4-diphenyl-3-propionoxyheptane (I-b) hydrochloride. This compound, prepared similarly to I-a in a yield of 80%, crystallized from acetone-ether in rosettes, m.p. 182–184°.

Anal. Calc'd for $C_{24}H_{34}ClNO_2$: C, 71.4; H, 8.5.
Found: C, 71.4; H, 8.3.

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[2] When methanol was used in lieu of acetic acid, absorption did not stop at one mole.

[3] All melting and boiling points are uncorrected.

[4] This material was generously supplied by the Mallinckrodt Chemical Works and Merck & Co., Inc.

The picrate crystallized from ethanol in yellow prisms of m.p. 168–169°.

Anal. Calc'd for $C_{30}H_{36}N_4O_9$: C, 60.4; H, 6.1.

Found: C, 60.6; H, 6.0.

Reaction of II with thionyl chloride. (a) *3-Chloro-6-dimethylamino-4,4-diphenylheptane (IV).* To a stirred solution of 5 g. of II in 20 cc. of dry benzene was added during five minutes (temperature 15–25°) 1.5 cc. of thionyl chloride. After standing for one hour at room temperature, the solution was diluted with 60 cc. of dry ether to give, on cooling at 5° overnight, 2.4 g. (40%) of IV hydrochloride, m.p. 113–117°. It was converted to the base (aqueous ammonia) which, after drying in ether, crystallized to a solid of m.p. 84–87°; needles from ligroin (b.p. 30–60°), m.p. 88–89.5°.

Anal. Calc'd for $C_{21}H_{28}ClN$: C, 76.5; H, 8.5.

Found: C, 76.8; H, 8.3.

The hydrochloride, prepared from the base in acetone-ether with hydrogen chloride gas, crystallized in clusters of needles of m.p. 120–121° (gas evolution).

Anal. Calc'd for $C_{21}H_{29}Cl_2N$: C, 68.8; H, 8.0.

Found: C, 68.6; H, 7.7.

Crystallization of this hydrochloride from methanol-ether gave prisms of m.p. 123–124° (gas evolution). Carbon-hydrogen analysis indicated one mole of solvate methanol which was indeterminate by loss in weight *in vacuo* at 98°.

Anal. Calc'd for $C_{21}H_{29}Cl_2N \cdot CH_3OH$: C, 66.3; H, 8.3.

Found: C, 66.6; H, 8.2.

The picrate, prepared from the base or either hydrochloride with aqueous alcoholic picric acid, crystallized from aqueous ethanol in yellow needles of m.p. 134.5–135°.

Anal. Calc'd for $C_{27}H_{31}ClN_4O_7$: C, 58.0; H, 5.6.

Found: C, 58.3; H, 5.5.

(b) *6-Dimethylamino-4,4-diphenylheptene-2 (III).* The filtrate from the 2.4 g. of IV hydrochloride was shaken with an excess of aqueous ammonia, dried over sodium sulfate, and acidified with hydrogen chloride gas. The resulting oil was cooled, washed with dry ether, and crystallized from ethyl acetate-ether to give 1.1 g. (18%) of a dihydrochloride[5] of III, m.p. 87–89°. It was converted to the base (aqueous ammonia-ether) which was distilled at 0.05 mm. (bath temperature 120–125°) to give a colorless, mobile oil.

Anal. Calc'd for $C_{21}H_{27}N$: C, 86.0; H, 9.3.

Found: C, 86.3; H, 9.4.

The hydrochloride, prepared by addition of one mole of hydrogen chloride to an acetone solution of the base followed by dilution with ether, or as described in footnote 5, crystallized from ethyl acetate in rectangular prisms, m.p. 133–135°, after drying in a vacuum desiccator (hygroscopic).

Anal. Calc'd for $C_{21}H_{28}ClN$: C, 76.4; H, 8.6.

Found: C, 75.8; H, 8.6.

The picrate, prepared from the base or either hydrochloride with aqueous ethanolic picric acid, melted at 112–114°; yellow prisms.

Anal. Calc'd for $C_{27}H_{30}N_4O_7$: C, 62.1; H, 5.8.

Found: C, 62.0; H, 5.8.

Reaction of II with thionyl chloride in boiling benzene. A mixture of 3.0 g. of II, 1.5 cc. of thionyl chloride and 12 cc. of dry benzene was refluxed for one-half hour and partitioned between ether and aqueous ammonia. The dried ether layer was neutralized with 1.5 g. of about 17% alcoholic hydrogen chloride and diluted with ligroin (b.p. 30–60°) to give, after seeding and cooling for two days (finally at 5°), 1.1 g. of the hydrochloride of III, m.p. 131–133°. The filtrate deposited 0.3 g. of the hydrochloride of IV, m.p. 117–119°.

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[5] *Anal.* Calc'd for $C_{21}H_{27}N \cdot 2HCl$: C, 68.8; H, 8.0; HCl (one mole), 9.96. Found: C, 69.6; H, 8.1; loss in wt. (77°, high vacuum), 8.71. This dihydrochloride is unstable and is converted to the monohydrochloride by evaporating its methanol solution to dryness and recrystallizing the residue from ethyl acetate.

Reaction of II with phosphorus pentachloride and with phosphorus pentoxide. To a stirred mixture of 5.0 g. of phosphorus pentachloride and 40 cc. of dry chloroform was added 3.5 g. of II in 20 cc. of chloroform during twenty minutes. The mixture was allowed to stand overnight, evaporated to dryness *in vacuo*, and the residue treated with cold, dilute sodium carbonate and ether. The ether was dried and acidified with hydrogen chloride to give a semisolid which crystallized from acetone-ether, yielding 1.0 g. of the dihydrochloride of III (*cf.* footnote 5), m.p. 85–90°. II (1.0 g.), 1.0 g. of phosphorus pentoxide and 5 cc. of dry toluene, refluxed for two hours, gave 0.4 g. of the dihydrochloride of III, m.p. 86–89°.

Reaction of II and of IV with hydriodic acid and phosphorus. II (1.0 g.), 2 cc. of 57% hydriodic acid, 0.4 g. of red phosphorus, and 5 cc. of acetic acid, refluxed for three hours, filtered, the filtrate evaporated to dryness, and the residue partitioned between 5% sodium hydroxide and ether, gave as described above, 0.3 g. of an unidentified fraction of needles and 0.3 g. of the dihydrochloride of III.

Similarly (reaction time one hour) 0.5 g. of IV gave 0.2 g. of III dihydrochloride.

3-Dimethylamino-1,1-diphenylbutane (VI) picrate. (a) *From V.* A mixture of 4 g. of V, 3.2 g. of potassium hydroxide, and 20 cc. of triethylene glycol was refluxed (bath temperature 220–230°) for four hours, diluted with water and ether, and the ether layer evaporated. To the residue was added 4 g. of picric acid in alcohol and the mixture heated to solution to give, on dilution with water and cooling, 5.4 g. (90%) of VI picrate, m.p. 138–140°. It crystallized from ethanol in yellow plates, of m.p. 138–139°.

Anal. Calc'd for $C_{24}H_{26}N_4O_7$: C, 59.7; H, 5.4.
Found: C, 60.0; H, 5.5.

The perchlorate crystallized from absolute ethanol in rods, m.p. 158–159°.

Anal. Calc'd for $C_{18}H_{24}ClNO_4$: C, 61.1; H, 6.8.
Found: C, 61.3; H, 6.8.

The hydrochloride, m.p. 151–155°, crystallized from ethyl acetate in prisms.

Anal. Calc'd for $C_{18}H_{24}ClN \cdot 0 \cdot 5H_2O$: C, 72.4; H, 8.4.
Found: C, 73.2; H, 8.2.

(b) *From 4-dimethylamino-2,2-diphenylpentanenitrile.* As described under (a) 1.0 g. of VIII (1),[4] 1.0 g. of potassium hydroxide, and 10 cc. of triethylene glycol, refluxed for ten hours, gave 1.3 g. of VI picrate, m.p. 134–136.5°.

Methiodide of VI (VII). The VI from 3.0 g. of picrate, 0.8 cc. of methyl iodide, and 5 cc. of methanol, allowed to stand for one hour, warmed to boiling, and diluted with ether, gave 2.3 g. (92%) of VII, m.p. 200–202°; prisms.

Anal. Calc'd for $C_{19}H_{26}IN$: C, 57.7; H, 6.7.
Found: C, 58.0; H, 6.6.

VII was also prepared in 90% yield on refluxing for six hours, 1.0 g. of V methiodide and 20 cc. of 25% sodium hydroxide.

Degradation of VII. (a) *Dibromo-1,1-diphenylbutane.*[6] A mixture of 5.0 g. of VII, 40 cc. of water, and freshly prepared silver oxide (from 10 g. of silver nitrate) was heated on the steam-bath for fifteen minutes, shaken for two hours, warmed again, filtered, and the filtrate evaporated to dryness *in vacuo*. Distillation of the residue at 100–105° (0.1 mm.) gave 2.2 g. (90%) of liquid X.[6] To 0.2 g. of this in 2 cc. of acetic acid was added dropwise 0.04 cc. of bromine and the solution diluted with a little water. Gradual cooling gave 0.2 g. (60%) of adduct, m.p. 55.5–57°; prisms from methanol, m.p. 55.5–56.5°.

Anal. Calc'd for $C_{16}H_{16}Br_2$: C, 52.2; H, 4.4.
Found: C, 52.5; H, 4.4.

(b) *1,1-Diphenylbutane (IX).* A mixture of 3.0 g. of X [see under (a)], 0.01 g. of platinum oxide, and 20 cc. of methanol absorbed one mole of hydrogen in one hour to give, on distillation of the product at 95° (0.05 mm.), 2.9 g. of IX, b.p. 102° (0.05 mm.), n_D^{20} 1.5601; lit. (6), b.p. 103–104° (0.05 mm.), n_D^{20} 1.5577.

Anal. Calc'd for $C_{16}H_{18}$: C, 91.4; H, 8.6.
Found: C, 91.5; H, 8.4.

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[6] No proof is offered for the location of the double bond in X.

Synthesis of 1,1-diphenylbutane. 1,1-Diphenyl-1-butanol was obtained in a yield of 60% from ethyl butyrate and phenylmagnesium bromide by the procedure of Schmidt and Hartmann (6). This carbinol (4.0 g.), 0.6 g. of 5% palladium charcoal, 35 cc. of acetic acid, and one drop of 60% perchloric acid absorbed 1.1 moles of hydrogen during five hours. The yield of evaporatively distilled IX was 3.4 g. (90%), b.p. 109.5–111° (0.5 mm.), n_D^{20} 1.5888. With palladium-barium sulfate the reduction time was twenty-four hours.

α,α-Diphenylvaleric acid. A mixture of 4.5 g. of α,α-diphenylvaleronitrile (1), 4.0 g. of potassium hydroxide and 23 cc. of triethylene glycol was refluxed for six hours. Ether and water were added, the aqueous phase was acidified, and the precipitate recrystallized from ethanol; yield of prisms 0.8 g., m.p. 150–152°. The acid was sublimed (130°/0.05 mm.) for analysis.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.5; H, 7.1.

From the ether phase, 0.7 g. of IX was obtained.

Nitration of 1,1-diphenylbutane. To 0.5 g. of IX (prepared by any of the three procedures above) cooled in water at 15° was added with shaking during three to five minutes, 1.5 cc. of nitric acid (*d*, 1.5). The mixture was warmed to homogeneity, diluted with water, cooled in ice, and the yellow viscous oil crystallized from 10 cc. of methanol to give 0.4 g. of *dinitro-1,1-diphenylbutane*, m.p. 113–118°. The analytical sample melted at 122–123°; prisms.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: N, 9.33. Found: N, 9.31.

SUMMARY

The hydrogenation of amidone to the carbinol, 6-dimethylamino-4, 4-diphenyl-3-heptanol, is described. O-Acyl derivatives of this carbinol are prepared in good yield, while reaction of the carbinol with chlorinating agents leads to a mixture of 3-chloro-6-dimethylamino-4,4-diphenylheptane and 6-dimethylamino-4,4-diphenylheptene-2.

In the reaction of amidone with alkali at 225°, scission of the ethyl keto group occurs.

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