[From the Daniel Sieff Research Institute, Weizmann Institute of Science]

SOME DERIVATIVES OF AMIDONE

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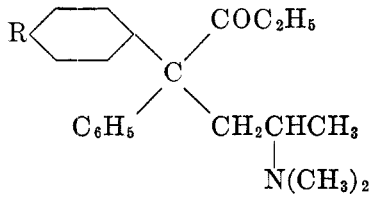
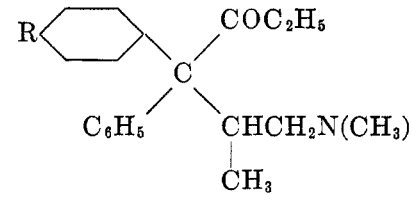
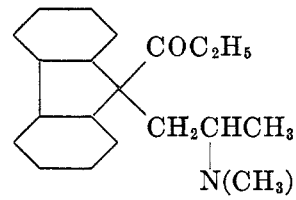
Since the biological properties of amidone (I, R = H) became known (1) only Thorp, Walton, and Ofner (2) have investigated systematically the influence of structural changes on the activity of the molecule; they condensed diphenylacetonitrile with aminoalkyl chlorides other than dimethylaminopropyl chloride and treated the condensation products with Grignard reagents other than ethylmagnesium bromide. In the present paper, variations in the diphenylmethyl moiety of the amidone molecule have been studied; the *p*-methoxy, *p*-methyl, and *p*-bromo derivatives of amidone (I, R = OCH_3, CH_3, Br, respectively) and its fluorene analog, 9-(β-dimethylaminopropyl)-9-propionylfluorene (II) have been prepared as well as 4,5-diphenyl-4-(β-dimethylaminopropyl)-3-pentanone (III), in which one of the phenyl groups of the amidone molecule is replaced by the benzyl radical.



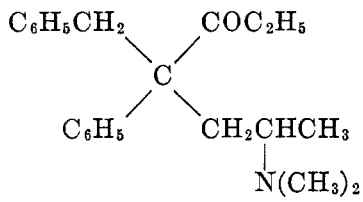
I



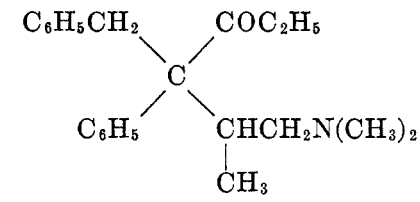
Ia



II



III

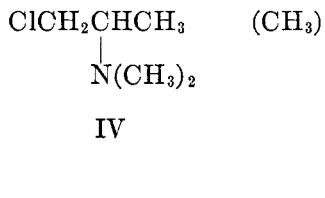


IIIa

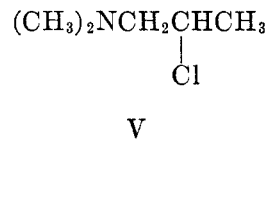
It was expected that these experiments would shed some light on the conditions of the simultaneous formation of the two isomers (I, Ia, R = H) which are obtained in the case of amidone[1] (3, 4) when diphenylacetonitrile is con-

[1] Easton, *et al.* (3), have also described a third isomeride of amidone, the structure of which has not yet been elucidated.

densed with either 2-dimethylamino-1-chloropropane (IV) or 1-dimethylamino-2-chloropropane (V), a fact which Schultz and Sprague (5) very plausibly ascribe to the transitory formation, from both (IV) and (V), of the ion (VI), capable of fission in two different ways (6, 7, 8). The diphenylacetonitrile anion causes this fission to take place in both directions to roughly the same extent. Our own observations have led to the same conclusion for the three *p*-substituted diphenylacetonitriles and for phenylbenzylacetonitrile: they lead to mixtures of the two isomers independently of whether (IV) or (V) is used as starting material. The only exception to this rule was observed in the synthesis of the fluorene derivative (II), in which only one product was obtained in excellent yield; the corresponding 9-(β-dimethylaminopropyl)-9-cyanofluorene—which is an oil—must, therefore, also have been a homogeneous substance.



IV



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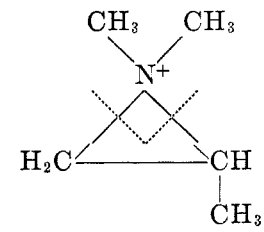
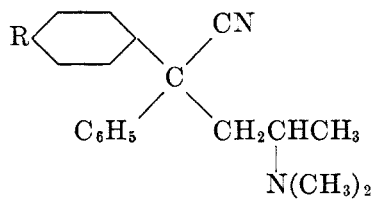
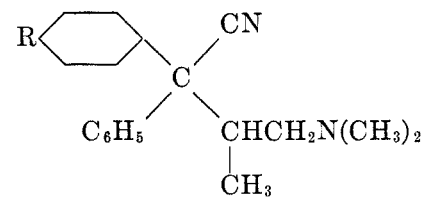


VI



VII



VIIa

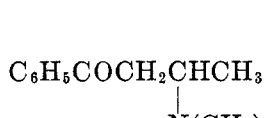
This may be due to the more pronounced acidic character of 9-cyanofluorene, as compared with diphenylacetonitrile and its derivatives, which causes one path of attack on (VI) to be preferred to the other in the same way as the chloride ion prefers the fission VI → V to VI → IV (5); the compound (IV) can thermally rearrange to (V), but not *vice versa*.

The nitriles (VII) and (VIIa) (R = OCH_3, CH_3, Br) and the nitrile corresponding to (III) and (IIIa), although analytically pure, did not crystallize and could not be separated into their constituent isomerides. They were treated with ethylmagnesium bromide and gave, upon subsequent hydrolysis, mixtures of the two isomeric ketones. In order to separate them, the—apparently quite different—basicity of the isomerides was utilised: when the mixtures were treated with half the theoretical amount of hydrochloric acid, one of the isomeric hydrochlorides precipitated; its purity (after recrystallization) was established by its crystallographic homogeneity, the sharpness of its melting point, and the possibility of its conversion into a homogeneous picrate. In no case has it been possible to isolate the second isomer, too, in a pure crystalline state.

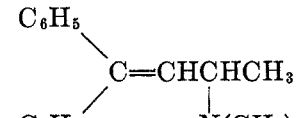
In the reaction of the nitriles (VII) and (VIIa) with ethylmagnesium bromide, the ketimines corresponding to (I) and (Ia) are formed initially; we have observed that the hydrolysis did not necessitate as stringent conditions as have been applied in the case of amidone and its isomer.

The impossibility of isolating both isomerides made it desirable to determine the side-chain structure of the crystalline products obtained. Of the three methods used hitherto in this series—that of Schultz, Robb, and Sprague (4); that of Easton, Gardner, and Stevens (9); and that of May and Mosettig (10)—the last seemed most adequate.

This method consists essentially in degradation through 3-dimethyl-1,1-diphenylbutane to 1,1-diphenylbutane; the latter was synthesized by an unambiguous method. The former has now been synthesized by an unambiguous method[2] of more general application, *viz:* by conversion of propenyl phenyl ketone to β-dimethylaminobutyrophenone (VIII) with dimethylamine, reaction of VIII with phenylmagnesium bromide, dehydration of the resulting carbinol to the olefin (IX), and catalytic hydrogenation of the latter.

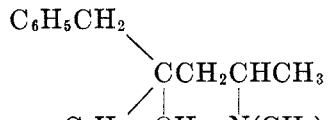


VIII

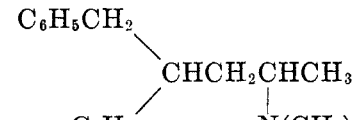


IX

By application of this method, it was, *e.g.*, possible to prove the structure (III) for the crystalline benzyl compound. Reaction of VIII with benzylmagnesium chloride gave the carbinol (X) which, by dehydration and subsequent hydrogenation was converted to 4,5-diphenyl-2-dimethylaminopentane (XI). The same compound was obtained by heating (III) with potassium hydroxide in triethyleneglycol. It is not unlikely, therefore, that all the crystalline isomers obtained in this investigation, correspond to formula I and not to Ia.



X



XI

Additional evidence is made available by a study of the ultraviolet absorption of the substance concerned. Strait, Kumler, Sah, Alpen, and Chang (12) have recently reported that amidone (I, R = H) has three bands at 2600 Å, at 3000 Å and below 2600 Å, whilst isoamidone (Ia, R = H) has only one band, near 2600 Å, attributed to phenyl absorption. It is unlikely that the explanation given by the authors, that in amidone the two phenyl groups are not linked to the same carbon atom, is correct (the above discussed degradation methods

[2] While this material was in press, a paper by Bockmühl and Erhart (11), reporting a somewhat similar method of synthesis, came to our attention.

appear to preclude this possibility)—but the observation in itself provides an empirical tool capable of differentiating between the isomers (I) and (Ia). Fig. 1 shows the absorption spectrum of the hydrochloride of amidone (I,

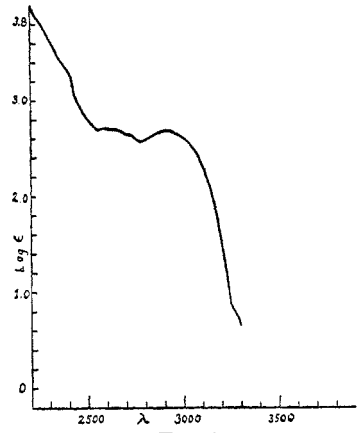


FIG. 1

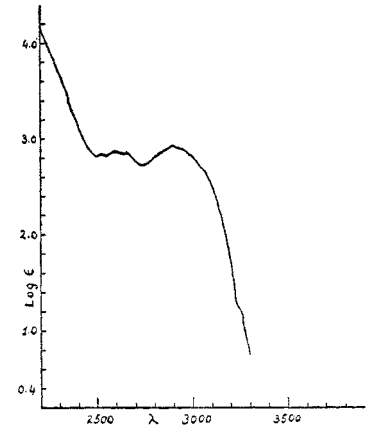


FIG. 2

FIG. 1. 2-DIMETHYLAMINO-4,4-DIPHENYL-5-HEPTANONE HYDROCHLORIDE (AMIDONE) (I, R = H), IN WATER

FIG. 2. 2-DIMETHYLAMINO-4-PHENYL-4-(*p*-TOLYL)-5-HEPTANONE HYDROCHLORIDE (I, R = CH_3), IN WATER

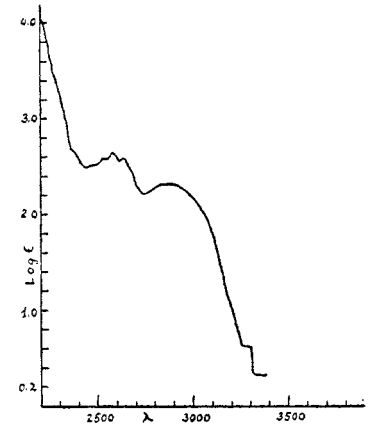


FIG. 3

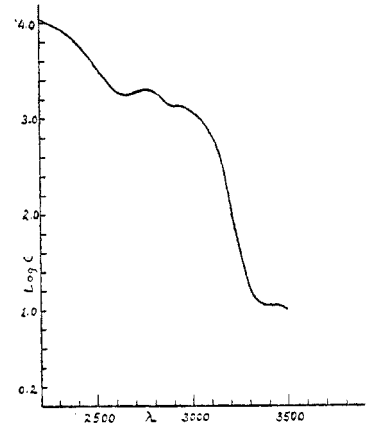


FIG. 4

FIG. 3. 2-DIMETHYLAMINO-4-PHENYL-5-BENZYL-5-HEPTANONE HYDROCHLORIDE (III), IN WATER

FIG. 4. 2-DIMETHYLAMINO-4-PHENYL-4-(*p*-METHOXYPHENYL)-5-HEPTANONE HYDROCHLORIDE (I, R = OCH_3), IN WATER

R = H) which is generally in agreement with the indications given by Strait and co-workers (12), and the spectra of the hydrochlorides of the tolyl compound (Fig. 2) and of the benzyl analog (Fig. 3) respectively are so similar to that of the parent substance that formulae (I, R = CH_3) and (III) appear

justified on spectro-analytical grounds, too. Also the methoxy-hydrochloride (Fig. 4) has a similar spectrum, so that it appears warranted to assign it formula (I, R = OCH_3). In the spectrum of the hydrochloride of the fluorene analog, too, (Fig. 5) the unexpected band at 3000 Å is present, which is an argument in favor of formula (II). It is interesting to note that the free base of (II) has practically the same spectrum as its hydrochloride (Fig. 6). Of course, in the fluorene compound one has to ascribe the very intense broad band at about 2650 Å to the absorption by the fluorene chromophor (13, 14, 15).

A detailed report on the physiological properties of the new compounds will be published elsewhere. An investigation of the fluorene derivative (II)

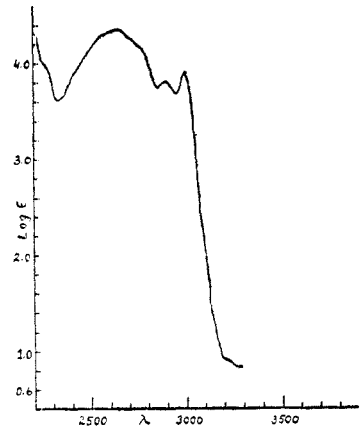


FIG. 5

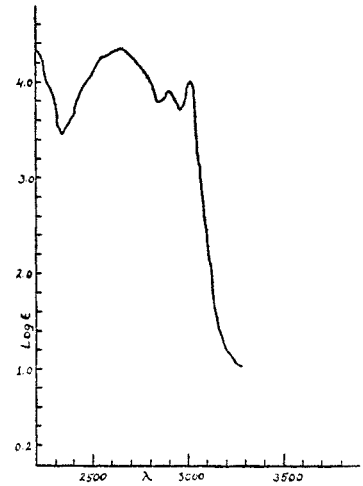


FIG. 6

FIG. 5. 9-(β-DIMETHYLAMINOPROPYL)-9-PROPIONYLFLUORENE HYDROCHLORIDE (II), IN WATER

FIG. 6. 9-(β-DIMETHYLAMINOPROPYL)-9-PROPIONYLFLUORENE (II), IN ALCOHOL

has been carried out in the Pharmacological Laboratories of Messrs. Geigy, Basle (Switzerland) through the courtesy of Dr. Krebser. The result was as follows: In doses of 0.5–5 mg./kg., the substance has a slight analgetic action, whilst amidone exhibits a strong analgetic effect in doses of 1.5 mg./kg. With 10 mg./kg. of the substance (II), tonic-clonic convulsions were observed (in rabbits). The average lethal dose was 62 mg./kg. (for amidone 17.5 mg./kg.) (intravenous injection in mice). The substance has also a spasmolytic effect, approximately of the same order as papaverine hydrochloride.

The help of Dr. Y. Hirshberg in determining the absorption spectra is gratefully acknowledged.

EXPERIMENTAL

The *diarylacetonitriles* were prepared from bromobenzyl cyanide by the Friedel-Crafts reaction. The method has been improved so as to give better yields, even of the parent substance, *diphenylacetonitrile*, which is thus obtained in a yield of 74% [50–51% according to Schultz, Robb, and Sprague (4)]. At 105–110°, bromine (17 cc.) was added to 35 g. of pure

(chlorine-free) benzyl cyanide with stirring over a period of thirty minutes. The heating was continued for another thirty minutes and the crude bromobenzyl cyanide was dissolved in 150 cc. of benzene. To this solution, 42 g. of powdered aluminum chloride was added within twenty to thirty minutes in portions of such size that the temperature rose to 45–50°. The reaction mixture was then heated for one hour at 60–65°, most of the benzene distilled off (maximum bath temperature 125°), and the hot residue treated with a mixture of 400 cc. of water, 400 g. of ice, and 20 cc. of hydrochloric acid. The resulting product was distilled with steam for twenty minutes and the reddish oil (which solidified upon cooling) redissolved in benzene. After washing with water and drying, the solvent was removed *in vacuo* and the diphenylacetonitrile purified by distillation under 0.2 mm. pressure; b.p. 121–125°, yield, 49 g. Crystallization from 1.2 parts of ethyl alcohol raised the m.p. from 67–69° to 75°; yield 43 g. (74%).

Phenyl-(p-tolyl)acetonitrile, prepared analogously, was an easily crystallizable oil, b.p. 164–170°/4 mm., m.p. 61°, after recrystallization from a small amount of ethyl alcohol; yield 65%. It has been synthesized before by a different method by Michael and Jeanprêtre (16, 17), who report b.p. about 240°/40 mm.; m.p. 61°.

Phenyl-(p-methoxyphenyl)acetonitrile. In its preparation, benzene was replaced by a solution of the theoretical quantity of anisole in three times its volume of nitrobenzene. Before decomposition, the reaction mixture was heated for one hour at 100–110°; b.p. 155–165°/2 mm.; yield 32%.

Phenyl-(p-bromophenyl)acetonitrile. Bromobenzyl cyanide was mixed with three times the theoretical quantity of bromobenzene and the aluminum chloride added. Reaction set in when the mixture was heated for a short while at 50°; it was completed at 100° (one hour). The oily product (b.p. 172–176°/0.8 mm.) crystallized; from ethyl alcohol clusters of needles, m.p. 82–83°; yield 80%.

Anal. Calc'd for $C_{14}H_{10}BrN$: C, 61.7; H, 3.7; N, 5.2.

Found: C, 61.5; H, 4.0; N, 5.2.

9-Cyanofluorene was most conveniently prepared according to Wislicenus and Russ (18) from formylfluorene oxime and thionyl chloride.

Phenylbenzylacetonitrile was obtained in 32% yield, when 38 g. of benzyl chloride was added, within forty-five minutes, to a mixture of benzyl cyanide (40 g.) and sodium butoxide (7 g. of sodium in 150 cc. of butanol) and the mixture was refluxed for four hours. Steam-distillation and vacuum-distillation of the residue, which was extracted previously with benzene, gave 23 g. of the desired nitrile, b.p. 158–170°/0.6 mm. The nitrile solidified spontaneously, and was recrystallized from alcohol; needles of m.p. 58° (19).

Whilst *2-dimethylamino-1-chloropropane* was prepared in the customary manner by reduction of ethyl β-dimethylaminopropionate to 2-dimethylamino-1-propanol and treatment of the latter with thionyl chloride in chloroform, an improved method was worked out for the preparation of *1-dimethylamino-2-chloropropane in toluene solution:* A mixture of 65 g. of dimethylamine, 65 g. of 1-chloro-2-propanol, and 90 g. of toluene was prepared at 5° and heated for ten hours in an autoclave at 95–100°. The crystals were filtered, washed with 250 cc. of toluene, and the combined toluene solutions added, with stirring, to a solution of 165 g. of thionyl chloride in 400 cc. of toluene, the temperature being kept at 10–15°. The reaction was complete after the resulting mass had been heated for six hours at 100°. The hydrochloride was washed with toluene; yield 90 g. (83%, calculated on the basis of chloropropanol). The product was dissolved in 90 cc. of water, and after addition of 125 cc. of toluene, was treated at 0° with 100 cc. of 50% potassium carbonate solution. The toluene solution was separated and the aqueous layer extracted with 75 cc. of toluene. The combined extracts were washed with 10 cc. of ice-water, twice with 10 cc. of saturated sodium chloride solution, and dried with sodium sulfate. To remove the last traces of water, 20 cc. of the filtered solution were distilled off and discarded. The solution contained approximately 56 g. of 1-dimethylamino-2-chloropropane.[3]

[3] For analysis, 10 g. of the solution is shaken with an excess of *N* hydrochloric acid and subsequently with water; the combined aqueous extracts are titrated.

9-(β-Dimethylaminopropyl)-9-cyanofluorene. At 45°, the suspension of 4.4 g. of sodamide in 75 cc. of toluene, containing 12 g. of 1-dimethylamino-2-chloropropane was treated, with stirring, with a solution of 19 g. of 9-cyanofluorene in 180 cc. of toluene, the temperature being kept at 50°. After heating for one hour at 55–60°, the temperature was raised slowly and the mixture refluxed for 75 minutes. After cooling and washing with water, the desired nitrile was extracted from the toluene layer with an excess of 15% hydrochloric acid, the aqueous solution washed once with toluene and made alkaline with an excess of 20% sodium hydroxide solution. The thick, yellow oil which separated was taken up with ether and the ethereal solution washed, dried, and distilled. Pale yellow, viscous oil, b.p. 168–170°/0.3 mm.; yield 21 g. (76%).

Anal. Calc'd for $C_{19}H_{20}N_2$: C, 82.6; H, 7.2; N, 10.2.

Found: C, 82.2; H, 7.1; N, 10.5.

In this and the other cases, summarized in Table I, the same product was obtained whether 1-dimethylamino-2-chloropropane or 2-dimethylamino-1-chloropropane was employed.

Amidones. The nitriles, prepared as described above, were directly treated with ethylmagnesium bromide and the resulting ketimines hydrolyzed in the manner outlined for the fluorene derivative (II).

TABLE I

BASIC NITRILES

MIXTURE OF	B.P., °C./MM.	YIELD, %	FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
VII and VIIa, R = OCH_3.....	162–168/0.1	44	$C_{20}H_{24}N_2O$	77.9	7.8	9.1	78.0	7.7	9.2
VII and VIIa, R = CH_3.....	148–155/0.1	69	$C_{20}H_{24}N_2$	82.2	8.2	9.5	82.0	8.5	9.1
VII and VIIa, R = Br.....	162–170/0.05	74	$C_{19}H_{21}BrN_2$	63.9	5.9	7.8	64.1	6.0	7.8
Phenylbenzyl-(β-dimethylaminopropyl)- and -(β-dimethylaminoisopropyl)-acetonitrile...	148–155/0.1	70	$C_{20}H_{24}N_2$	82.2	8.2	9.5	82.3	8.1	9.5

9-(β-Dimethylaminopropyl)-9-propionylfluorene (II). To a boiling solution, prepared from 6.5 g. of magnesium and 26 cc. of ethyl bromide in 60 cc. of ether, 20 g. of 9-(β-dimethylaminopropyl)-9-cyanofluorene in 100 cc. of benzene was added, and most of the ether was distilled off simultaneously. The reaction mixture was then refluxed for 10 hours, decomposed with an ice-cold ammonium chloride solution, and extracted with 30 cc. of cold, 25% sulfuric acid. The acid extract was washed once with benzene and after the further addition of 50 cc. of sulfuric acid, heated at 100° for 90 minutes. After cooling, the solution was made alkaline with 33% aqueous sodium hydroxide solution and the oil which separated was taken up in benzene, b.p. 152–158°/0.6 mm.; yield 14.5 g. (65%). The oil solidified upon standing; from 85% alcohol, m.p. 66–68°. The substance was characterized as the *hydrochloride*, which was obtained in 86% yield when the base in isopropanol was treated with an isopropanolic hydrogen chloride solution. After recrystallization from the same solvent, it had m.p. 262–264°.

Anal. Calc'd for $C_{21}H_{26}ClNO$: N, 4.1. Found: N, 4.5.

The other basic ketones were prepared analogously; as already pointed out, the hydrochlorides corresponding to formula (I) were obtained by adding only half of the theoretical quantity of isopropanolic hydrogen chloride solution to the solution of the basic ketones in isopropyl alcohol and precipitating with ether. When the filtrates were treated with isopropanolic hydrogen chloride, no precipitate was obtained, and evaporation of the

solutions gave reddish, hygroscopic powders, from which no defined substance could be isolated. The crystalline hydrochlorides were converted into the picrates with sodium picrate in alcohol.

The mixture of the basic ketones (III and IIIa), which was obtained in 75% yield, boiled at 174–178°/0.2 mm.; it gave the correct analytical figures.

Anal. Calc'd for $C_{22}H_{29}NO$: C, 81.7; H, 9.0; N, 4.3.
Found: C, 82.0; H, 9.2; N, 4.5.

The *hydrochloride*, prepared in the manner indicated above, was an oil which had to be triturated with ether at 0° for several days, before crystallizing. Recrystallization from butyl acetate gave crystals of m.p. 100–103° which apparently contained one mole of water of crystallization.

Anal. Calc'd for $C_{22}H_{30}ClNO \cdot H_2O$: C, 70.0; H, 8.0.
Found: C, 70.3; H, 8.5.

TABLE II

BASIC KETONES (I)

MIXTURES OF	B.P., °C./MM.	YIELD, %	HYDROCHLORIDE OF	RECRYSTALLIZED FROM	M.P., °C.	ANALYSIS					
						Calc'd			Found		
						C	H	N	C	H	N
I, Ia (R = CH_3)	175–180/2	82	I, $C_{22}H_{29}NO \cdot HCl$	butyl acetate	202–204	73.5	8.4	3.9	73.7	8.6	4.2
I, Ia (R = OCH_3)	160–163/0.1	60	I, $C_{22}H_{29}NO_2 \cdot HCl$	butyl acetate	162–163	70.4	8.0	3.7	70.4	8.1	4.0
I, Ia (R = Br)	175–180/0.1	80	I, $C_{21}H_{26}BrNO \cdot HCl$	butyl acetate	205–207	59.4	6.4	3.3	58.9	6.7	3.4

PICRATE, M.P., °C.	FORMULA	ANALYSIS					
		Calculated			Found		
		C	H	N	C	H	N
138–140	$C_{28}H_{32}N_4O_8$; from ethanol	60.9	5.8	10.1	60.5	5.8	10.0
178–179	$C_{28}H_{32}N_4O_9$	59.1	5.6	9.9	58.7	5.6	9.8
153–154	$C_{27}H_{29}BrN_4O_8$; from ethanol	52.5	4.6	9.1	52.0	4.7	9.4

Drying at 90–95° (*in vacuo*) gave the anhydrous hydrochloride, which melted at 145–147°. The *picrate* had m.p. 164–166° after several recrystallizations from ethyl alcohol and butyl acetate. From the mother liquors, a small amount of a second [isomeric (IIIa)?] *picrate*, m.p. 152°, could be isolated.

Anal. Calc'd for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.8; N, 10.1.
Found: C, 60.5; H, 5.8; N, 10.0.

From the picrate of m.p. 164–166°, the basic ketone (III) could be isolated in pure form, by treatment with sodium hydroxide solution. Recrystallization from 90% methanol gave well-shaped crystals of m.p. 67–68°.

Anal. Calc'd for $C_{22}H_{29}NO$: N, 4.3. Found: N, 4.7.

β-Dimethylaminobutyrophenone (VIII) (11). A mixture of 42 g. of propenylphenylketone (20) and 60 g. of toluene was cooled at 5–10° and after the addition of 30 g. of dimethylamine, was heated at 60° for eighteen hours in an autoclave. The solvent was removed *in vacuo* and the residue heated at 70° for two hours. The crude product (45 g.) was used for the reaction with Grignard compounds, as (VIII) tends to decompose into the components

during all attempts at purification. Its *picrate*, from ethyl alcohol, m.p. 122–123°, could be isolated in a fairly pure state.

Anal. Calc'd for $C_{18}H_{20}N_4O_8$: C, 51.4; H, 4.8; N, 13.3.

Found: C, 52.4; H, 5.1; N, 12.7.

1,1-Diphenyl-3-dimethylamino-1-butanol (11). To a Grignard solution, prepared from 1.2 g. of magnesium and 8 g. of bromobenzene, there was added, with cooling, an ethereal solution of 9.5 g. of the crude amino ketone. After refluxing the mixture for thirty minutes, it was decomposed with ice and ammonium chloride, and the ethereal solution extracted with dilute hydrochloric acid from which the basic alcohol was liberated by treatment with aqueous sodium hydroxide solution and ether. The oily product crystallized upon standing; from ethanol, m.p. 120–122°; yield 0.8 g. *Picrate*, from ethyl alcohol, m.p. 160–162°.

Anal. Calc'd for $C_{24}H_{26}N_4O_8$: N, 11.2. Found: N, 11.1.

The *carbinol* could not be reduced to 3-dimethylamino-1,1-diphenylbutane by catalytic hydrogenation in presence of perchloric acid (21), using palladium or Raney nickel as catalyst.

1,1-Diphenyl-3-dimethylamino-1-butene (IX). The above carbinol (1 g.) was heated with potassium hydrogen sulfate (2 g.) at 150–160° for ninety minutes. The reaction product was dissolved in water and the solution treated with sodium hydroxide solution and ether. The oily product was characterized as its *picrate*, m.p. 195–196°.

Anal. Calc'd for $C_{24}H_{24}N_4O_7$: N, 11.7. Found: N, 11.5.

1,1-Diphenyl-3-dimethylaminobutane. The olefin (IX) was hydrogenated in ethanolic solution at room temperature and atmospheric pressure, using nickel as catalyst. The theoretical amount of hydrogen was absorbed in six hours. The *picrate* obtained from the filtered solution had m.p. 138–140° and was identical with the product according to May and Mosettig (10).

4,5-Diphenyl-2-dimethylamino-4-pentanol (X). The reaction between β-dimethylaminobutyrophenone (VIII) and benzylmagnesium chloride was carried out as above, but at 0°. After two hours' standing at room temperature, the product was decomposed with ice and ammonium chloride and the ethereal layer extracted with dilute acetic acid. The aqueous solution was made alkaline with potassium carbonate solution and extracted with benzene. The amino alcohol crystallized spontaneously; from ethyl alcohol, m.p. 94–95°; yield, 28%. *Picrate*, from ethyl alcohol, m.p. 135–137°.

Anal. Calc'd for $C_{25}H_{28}N_4O_8$: C, 58.6; H, 5.5; N, 10.95.

Found: C, 58.8; H, 6.1; N, 11.7.

4,5-Diphenyl-2-dimethylaminopentane (XI). (a) The amino alcohol (X) was dehydrated with potassium hydrogen sulfate, as described above, and the crude dehydration product[4] hydrogenated in ethyl alcohol with a Raney nickel catalyst. The hydrogenation required thirty minutes. The filtered solution was treated with picric acid and the *picrate* recrystallized from a mixture of ethyl alcohol and acetone; m.p. 168–170°.

Anal. Calc'd for $C_{25}H_{28}N_4O_7$: C, 60.5; H, 5.65; N, 11.3.

Found: C, 61.10; H, 6.3; N, 11.7.

(b) The ketone (III) was degraded in the following manner: One gram of the pure base (m.p. 67–68°), 0.8 g. of potassium hydroxide, and 5 cc. of triethyleneglycol were heated for four hours at 220–225°. The reaction product was cooled and treated with ether and water, and the residue of the ethereal layer taken up with 20 cc. of alcoholic picric acid solution; then 20 cc. of water was added. Three crystallizations of the precipitate from an alcohol-acetone mixture (10:1) gave the *picrate* of m.p. 168–170° which was not depressed by admixture of the synthetic substance.

SUMMARY

The 4-methoxy, 4-bromo, and 4-methyl derivatives of amidone were synthesized in the manner used in the synthesis of the parent substance. Likewise,

[4] No attempt was made to purify the dehydration product or to determine whether the double bond was situated in 4,5 or in 3,4.

9-(β-dimethylaminopropyl)-9-propionylfluorene (II) and 4,5-diphenyl-4-(β-dimethylaminopropyl)-3-pentanone (III) were synthesized.

With the exception of the fluorene compound (II), mixtures of isomers, corresponding in structure to amidone (I, R = H), and isoamidone (Ia, R = H), were obtained, from which one isomer could be isolated in pure form. It has been proven or at least made probable that these crystalline compounds are analogous to amidone and not to the isocompound. For the proof of these structures, the ultraviolet absorption spectra of the new substances have been utilized.

The pharmacological properties of the fluorene derivative (II) are reported.

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