in 90 ml. of carbon dioxide-free water and the mixture was allowed to stand at room temperature under nitrogen. A control solution of 2.0 g. of D-glucose in 100 ml. of water, but containing no resin, also was prepared. After 188 hours, the isomerization mixture was filtered from the resin, with washing, and was concentrated at reduced pressure to a volume of 20 ml. The control solution was similarly concentrated. Both solutions then were treated at 0° with solutions containing 1 ml. of phenylhydrazine, 4 ml. of water and 5 drops of acetic acid. After 18 hours at 0°, filtration, washing and drying were performed as described previously.[4] The control solution yielded no product, whereas the isomerization solution yielded 60.5 mg. of D-mannose phenylhydrazone, m.p. 190–191°. When this yield is corrected for destruction of sugar to acidic products[1] and for the solubility of the phenylhydrazone,[4] the calculated production of D-mannose is 3.8% of the total remaining sugar. This value is in reasonable agreement with that observed[3,4] from D-glucose in dilute aqueous alkali.

The identity of the D-mannose phenylhydrazone was confirmed by converting it to the known anhydro-*O*-tetraacetate,[5] m.p. and m.m.p. 123–124°; $[\alpha]^{25}D$ 12° in pyridine (*c* 4).

(5) M. L. Wolfrom and Mary Grace Blair, THIS JOURNAL, **68**, 2110 (1946). The author is indebted to Dr. Blair for an authentic sample of this compound.

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Some Amines Derived from 3-Phenyl-1-indanone

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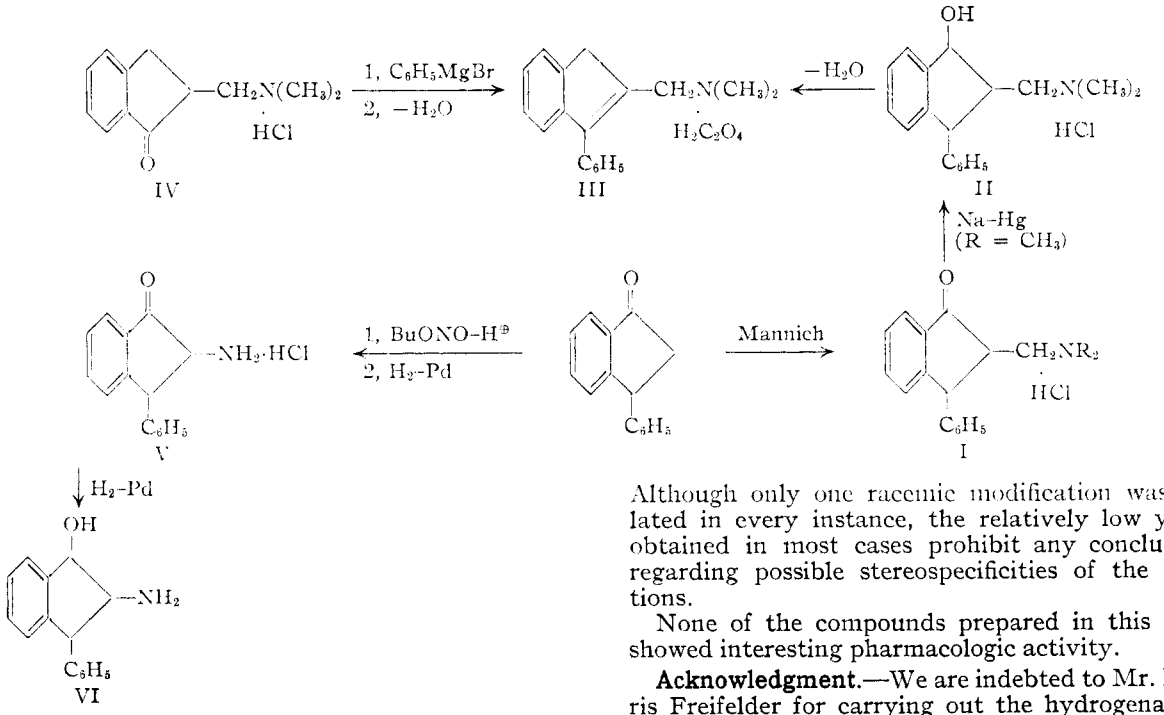
Amines derived from the Mannich reaction of 1-indanone show definite pharmacologic activity.[1,2] For this reason similar products derived from 3-phenyl-1-indanone were prepared in the present work which is summarized in the accompanying flow sheet. The Mannich products I obtained from the four amines, dimethylamine, diethylamine, piperidine and morpholine, were all formed in poor yield and seemed to be even less stable than the simpler Mannich products from 1-indanone (type IV). Like the latter,[2] the hydrochlorides of type I also split off the starting amine hydrochlorides at or near their melting points. Reduction with sodium amalgam of the Mannich product from dimethylamine (I, R = CH_3) led to the carbinol II which on dehydration gave the same indene derivative III (isolated as the bioxalate) obtained by dehydration of the phenyl Grignard adduct of IV. Rearrangement of the double bond, formed initially on dehydration of II, to the position shown in III must occur as a result of stabilization gained from conjugation with both aromatic rings.[3]

Stepwise catalytic hydrogenation of 2-isonitroso-3-phenyl-1-indanone led first to the aminoindanone V isolated as the hydrochloride, and finally to the aminoalcohol VI isolated in the form of the solid free base. All attempts to prepare N-disubstituted amines of type V by reaction of 2-bromo-3-phenyl-1-indanone with secondary amines failed. Likewise, reduction of this bromoketone with aluminum isopropoxide to 2-bromo-3-phenyl-1-indanol followed by reaction with secondary amines failed to produce N-disubstituted analogs of VI.

Most of the compounds prepared in this work contain either two or three asymmetric carbon atoms. The authors feel that all of the products isolated were relatively pure diastereoisomers.



Although only one racemic modification was isolated in every instance, the relatively low yields obtained in most cases prohibit any conclusions regarding possible stereospecificities of the reactions.

None of the compounds prepared in this work showed interesting pharmacologic activity.

Acknowledgment.—We are indebted to Mr. Morris Freifelder for carrying out the hydrogenations and to Mr. E. F. Shelberg for the microanalyses.

Experimental

2-Dimethylaminomethyl-3-phenyl-1-indanone Hydrochloride (I, R = CH_3).—To a stirred refluxing solution of 31.2 g.

(1) K. Hoffmann and H. Schellenberg, *Helv. Chim. Acta*, **27**, 1782 (1944); U. S. Patent 2,441,069 (1948), 2,479,744 (1949).

(2) J. O. Jilek, M. Borovička and M. Protiva, *Coll. Czech. Chem. Comm.*, **18**, 257 (1953).

(3) Compare C. F. Koelsch and R. A. Scheiderbauer, THIS JOURNAL, **65**, 2311 (1943).

(0.15 mole) of 3-phenyl-1-indanone,[4] 50 g. (0.61 mole) of dimethylamine hydrochloride and 0.36 cc. of concd. hydrochloric acid in 60 cc. of absolute ethanol was added in portions, over a period of 105 minutes, 13 g. (0.43 mole) of paraformaldehyde. After addition was complete, refluxing and stirring was continued for another 40 minutes, the mixture was cooled, and then poured into ice containing 3 cc. of concd. hydrochloric acid. Insoluble material was removed by extraction with ether and the aqueous layer was made alkaline with 2 *N* sodium hydroxide solution, a low temperature being assured by the simultaneous addition of ice. The precipitated oil was taken up in ether, which was washed with water and dried over anhydrous magnesium sulfate. Filtration and treatment of the filtrate with excess ethereal hydrogen chloride precipitated the hydrochloride of the product (I, R = CH_3) as an oil which soon solidified to give 22.7 g., m.p. 125–135°. Two recrystallizations from methanol–ether gave 15.3 g. (34%) of a white crystalline powder, m.p. 138–140°. At this temperature the product seems to split off dimethylamine hydrochloride to form a cloudy melt which does not become entirely clear until the melting point (167–169°) of the latter is reached.

Anal. Calcd. for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.29; H, 6.49; N, 4.74.

Replacing the dimethylamine hydrochloride in the above procedure by the hydrochlorides of diethylamine, piperidine and morpholine gave the three corresponding Mannich products as follows:

2-Diethylaminomethyl-3-phenyl-1-indanone Hydrochloride (I, R = C_2H_5), m.p. 120–121° (13% yield). *Anal.* Calcd. for $C_{20}H_{24}ClNO$: N, 4.24. Found: N, 3.89.

2-Piperidinomethyl-3-phenyl-1-indanone Hydrochloride (I, NR_2 = piperidino), m.p. 155–156° (12% yield). *Anal.* Calcd. for $C_{21}H_{24}ClNO$: N, 4.09. Found: N, 4.02.

2-Morpholinomethyl-3-phenyl-1-indanone Hydrochloride (I, NR_2 = morpholino), m.p. 150–151° (30% yield). *Anal.* Calcd. for $C_{20}H_{22}ClNO_2$: C, 69.85; H, 6.46; N, 4.06. Found: C, 70.04; H, 6.67; N, 3.96.

2-Dimethylaminomethyl-3-phenyl-1-indanol Hydrochloride (II).—To a vigorously stirred solution of 15 g. of the ketone hydrochloride I (R = CH_3) in a mixture of 75 cc. of methanol and 225 cc. of water, cooled in an ice-bath, was added in portions, over a period of 40 minutes, 300 g. of 5% sodium amalgam. During this period about 75 cc. of 50% aqueous acetic acid solution was added dropwise in order to maintain the *p*H of the reaction mixture in the range four to six as measured at intervals by means of test paper. Also the temperature of the reaction was kept in the range 5–8°. Then 40 cc. more 50% acetic acid was added in one portion and stirring in an ice-bath was continued for another 75 minutes. The cloudy reaction mixture was decanted from the mercury and clarified by ether extraction. The aqueous layer was then made alkaline by addition of 20% sodium hydroxide solution and the precipitated base was taken up in ether, washed with water to neutrality and dried over anhydrous magnesium sulfate. Filtration and addition to the filtrate of excess ethereal hydrogen chloride precipitated 11.2 g. of a crude hydrochloride, m.p. 195–205°. Two recrystallizations from dry isopropyl alcohol gave 4.2 g., m.p. 238.5–240°.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30; N, 4.61. Found: C, 70.63; H, 7.02; N, 4.59.

2-Dimethylaminomethyl-3-phenylindene Bioxalate (III).

A. By Dehydration of II.—A solution of 1 g. of the indanol II in a mixture of 2 cc. of concd. hydrochloric acid and 8 cc. of glacial acetic acid was refluxed for 15 minutes and then concentrated *in vacuo* to dryness. The residue was dissolved in water and a small amount of insoluble material was removed by extraction with ether. The aqueous layer was made alkaline with excess concd. ammonium hydroxide and the precipitated base was taken up in ether, washed to neutrality with water and dried over anhydrous magnesium sulfate. Filtration and treatment of the filtrate with a slight excess of oxalic acid dissolved in dry ether precipitated 1 g. of an oxalate, m.p. 163–170°. Two recrystallizations from dry ethanol–ether gave 2-dimethylaminomethyl-3-phenylindene bioxalate (III), m.p. 183–185°.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.78; H, 6.34.

The hydrochloride of III, m.p. 169–170°, was also prepared but could not be obtained analytically pure.

Anal. Calcd. for $C_{18}H_{20}ClN$: C, 75.64; H, 7.05; N, 4.90. Found: C, 74.44; H, 6.98; N, 4.99.

B. From 2-Dimethylamino-1-indanone (IV) and Phenylmagnesium Bromide.—Treatment of IV with phenylmagnesium bromide according to the procedure outlined by Hoffmann and Schellenberg[1] for the corresponding piperidino derivative gave III which was isolated by distillation of the free base, b.p. 136–137° (0.5 mm.), m.p. 65–67°, which was converted to the bioxalate, m.p. 184–186°.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.98; H, 5.84.

A mixture of this product with that prepared according to method A, m.p. 183–185°, showed no depression of melting point.

2-Amino-3-phenyl-1-indanone (V).—A suspension of 5.9 g. of 2-isonitroso-3-phenyl-1-indanone[5] in 250 cc. of absolute ethanol containing 3 g. of hydrogen chloride was hydrogenated for four hours at room temperature and 35 pounds pressure in the presence of 0.6 g. of 20% palladium-on-charcoal. After removal of the catalyst by filtration, the filtrate was concentrated to a volume of about 20–25 cc. and the crude product (5.5 g., 86%) was precipitated by the addition of five volumes of dry ether. For analysis, purification was accomplished by conversion to the oily free base, regeneration of the hydrochloride and trituration of the latter with dry acetone in order to remove a purple colored impurity which formed in the process. Two recrystallizations of this hydrochloride from isopropylalcohol–ether gave pure V in the form of a white micro-crystalline powder which melted with decomposition over a range above 250°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.10; H, 5.38; N, 5.47.

2-Amino-3-phenyl-1-indanol (VI).—A solution of 5.5 g. of 2-amino-3-phenyl-1-indanone hydrochloride (V) in 200 cc. of water was hydrogenated, in the presence of 1 g. of 10% palladium-on-charcoal, at room temperature and 40 pounds pressure for 20 hours. After removal of the catalyst by filtration, the solvent was removed by distillation *in vacuo* and replaced with acetone. Addition of ether precipitated the product (5.5 g., m.p. 100–110°) which could not be purified readily. However, conversion to the solid free base and recrystallization from benzene gave 3.4 g. of VI, m.p. 150–152°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.71; H, 6.70; N, 5.61.

2-Bromo-3-phenyl-1-indanone.—Although previously reported,[6,7] this compound does not appear to have been prepared by direct bromination of 3-phenyl-1-indanone. To a solution of 35 g. (0.167 mole) of 3-phenyl-1-indanone in 450 cc. of dry ether was added, dropwise with stirring, a solution of 26.7 g. (0.167 mole) of bromine in 225 cc. of chloroform. The temperature was maintained at 18–20° during the addition, after which the reaction mixture was washed with water to neutrality and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent by distillation gave 49.5 g. of crude product which, after two recrystallizations from hexane, yielded pure 2-bromo-3-phenyl-1-indanone (39.5 g., 82%), m.p. 87–88°.

2-Bromo-3-phenyl-1-indanol.—A solution of 12 g. (0.0415 mole) of 2-bromo-3-phenyl-1-indanone and 8.5 g. (0.0415 mole) of aluminum isopropoxide in 60 cc. of dry isopropyl alcohol was boiled for 2.5 hours, during which acetone, formed in the reaction, was distilled (together with some isopropyl alcohol) through a fractionating column, at a rate of 4–6 drops per minute. At the end of this time the reaction mixture, which had developed a mushy consistency, was cooled and treated with a cold solution of 18 cc. of concd. hydrochloric acid in 88 cc. of water. The organic layer was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether gave a dark oil which was taken up in ethyl acetate, treated with pentane and cooled. There was deposited a small yield of crude product which was crystallized once from heptane to give 1.6 g. of 2-bromo-3-phenyl-1-indanol, m.p. 129.5–130°.

(4) C. F. Koelsch, H. Hochmann and C. D. LeClaire, THIS JOURNAL, **65**, 59 (1943).

(5) C. F. Koelsch, *ibid.*, **58**, 1321 (1936).

(6) E. P. Kohler, G. L. Heritage and M. C. Burnley, *Am. Chem. J.*, **44**, 60 (1910).

(7) R. Weiss and S. Luft, *Monatsh.*, **48**, 337 (1927).

Anal. Calcd. for $C_{15}H_{13}BrO$: C, 62.29; H, 4.52. Found: C, 62.39; H, 4.39.

Distillation of the liquid residue revealed that it consisted of a complex mixture of by-products.

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p-Nitroacetophenone in the Mannich Reaction

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Of the three nuclear nitroacetophenones, only the *ortho*[1] and *meta*[1,2] have been reported as participants in the Mannich reaction. Investigation of the chemistry of *p*-nitroacetophenone has shown that the Mannich reaction proceeds quite satisfactorily, giving the expected β-(di)-alkylamino-*p*-nitropropiophenones, generally in fair yields.

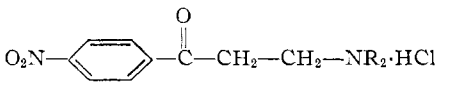
In Table I are recorded the results of a number of reactions involving primary and secondary amines with formaldehyde and *p*-nitroacetophenone. The general procedure was that described by Maxwell[3] for acetophenone. In some cases the amine hydrochloride was employed, in others the amine hydrochloride was prepared *in situ* by addition of one equivalent of concentrated hydrochloric acid to the amine. The method of choice appears to be dictated by the availability of the amine or its hydrochloride. Under the conditions used, diisopropylamine and β,β′-iminodipropionitrile failed to react, and isopropylamine and dimethallylamine gave only poor yields. Methylamine yielded the tertiary amine by reaction of two moles of ketone and two moles of formaldehyde; the other primary amines yielded the secondary Mannich base as the only isolable product.

A few reactions of these Mannich bases suggest normal reactivity for this type of compound. Catalytic reduction over palladium-on-carbon gave the *p*-aminoketones; over platinum an amount of hydrogen corresponding to reduction of nitro to amino and ketone to alcohol was absorbed, although no crystalline products could be isolated. In the latter case the absorption of the first three moles of hydrogen was approximately ten times as fast as that of the fourth mole. In the one example tried, the expected pyrazoline formed on treatment of the Mannich base with phenylhydrazine.

Experimental

β-(Di)-alkylamino-*p*-nitropropiophenone Hydrochlorides (See Table I).—Mannich reactions with *p*-nitroacetophenone were carried out in a manner similar to that described for acetophenone.[3] Method A refers to experiments in which the amine hydrochloride was used, method B to those in which the amine plus one equivalent of concentrated hydrochloric acid was used.

TABLE I



NR_2[a]	Yield, %	Method[b]	M.p., °C. (cor.)	Recryst. solvent	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$N(CH_3)_2$	64	A	187.5–188.5	EtOH	$C_{11}H_{14}N_2O_3\cdot HCl$	51.1	51.2	5.8	5.9
$N(C_2H_5)_2$	60	A	147–152	EtOH	$C_{13}H_{18}N_2O_3\cdot HCl$	54.4	54.8	6.7	6.8
NC_4H_8	37	B	182.5–185	*n*-BuOH	$C_{13}H_{16}N_2O_3\cdot HCl$	54.8	55.1	6.0	6.2
NC_5H_{10}	62	B	198–200	*i*-PrOH–Me_2CO	$C_{14}H_{18}N_2O_3\cdot HCl$	56.3	56.4	6.4	6.5
NC_4H_8O	51	A	207–209.5	EtOH–H_2O	$C_{13}H_{16}N_2O_4\cdot HCl$	52.1	52.4	5.7	5.8
$N(n\text{-}C_4H_9)_2$	53	B	150–210 dec.	*i*-PrOH–H_2O	$C_{17}H_{26}N_2O_3\cdot HCl$	59.5	59.5	7.9	7.9
$N(C_2H_4OH)_2$	58	B	138–140	EtOH	$C_{13}H_{18}N_2O_5\cdot HCl$	49.0	49.1	6.0	5.9
$N(CH_2\text{—}CMe{=}CH_2)_2$	8	B	138–140.5	*i*-PrOH–H_2O	$C_{17}H_{22}N_2O_3\cdot HCl$	60.2	60.7	6.6	6.8
$N<^{CH_3}_{CH_2C_6H_5}$	70	A	186–187	MeOH	$C_{17}H_{18}N_2O_3\cdot HCl$	61.0	61.1	5.7	6.0
$N<^{C_2H_5}_{C_2H_4OH}$	28	B	124.5–127	MeOH	$C_{13}H_{18}N_2O_4\cdot HCl$	51.6	51.8	6.3	6.7
$NHCH_2C_6H_5$	68	A	219.5–221 dec.	EtOH–Me_2CO	$C_{16}H_{16}N_2O_3\cdot HCl$	59.9	60.2	5.3	5.6
$NHCH(CH_3)_2$	10	B	207–209 dec.	MeOH–Me_2CO	$C_{12}H_{16}N_2O_3\cdot HCl$	52.8	53.1	6.3	6.5
NHC_6H_{11}	52	B	191–195 dec.	MeOH–*i*-PrOH	$C_{15}H_{20}N_2O_3\cdot HCl$	57.6	58.0	6.8	6.8
$NHC_8H_{17}(t)$	57	A	208–209	MeOH	$C_{17}H_{26}N_2O_3\cdot HCl$	59.6	59.7	7.9	7.9
$NHCH_2CO_2C_2H_5$	33	A	177–179	*i*-PrOH–H_2O	$C_{13}H_{16}N_2O_5\cdot HCl$	49.3	49.9	5.4	5.7

[a] NC_4H_8 = 1-pyrrolidyl; NC_5H_{10} = 1-piperidyl; NC_4H_8O = 4-morpholinyl; C_6H_{11} = cyclohexyl; C_8H_{17}-*t* = 1,1,3,3-tetramethylbutyl. [b] See Experimental.

β,β′-Methyliminodi-(*p*-nitropropiophenone)-Hydrochloride.—A solution of 165 g. (1.0 mole) of *p*-nitroacetophenone, 30 g. (1.0 mole) of paraformaldehyde and 33.9 g. (0.5 mole) of methylamine hydrochloride in 160 ml. of 95% ethanol was refluxed for three hours. The clear hot solution was poured into 800 ml. of acetone; crystals formed on cooling. Filtration gave 38 g. of solid, m.p. 195–200°. Evaporation of the filtrate and crystallization of the residue from methanol gave an additional 66 g. of solid, m.p. 195–200° (total yield, 49%). Recrystallization from dimethylformamide entailed a large loss, but with little improvement in melting point; an analytical sample thus prepared melted at 198–201° dec.

Anal. Calcd. for $C_{19}H_{19}N_3O_6\cdot HCl$: C, 54.1; H, 4.8. Found: C, 54.2; H, 5.4.

Unreacted *p*-nitroacetophenone (42 g., 25%) was recovered from the methanol mother liquors.

β-Amino-β-dimethylaminopropiophenone Hydrochloride.—β-Dimethylamino-*p*-nitropropiophenone hydrochloride (19.4 g., 0.075 mole) was hydrogenated in 200 ml. of methanol over 0.5 g. of 5% palladium-on-carbon. At three atmospheres, hydrogen absorption was 89% complete (for reduction of the nitro group only) in two hours. The reduc-

(1) C. Mannich and M. Dannehl, *Arch. Pharm.*, **276**, 206 (1938).

(2) H. B. Wright and M. Freifelder, THIS JOURNAL, **71**, 1513 (1949).

(3) C. R. Maxwell, *Org. Syntheses*, **23**, 30 (1943).