148°. The **hydrochloride** melted at 149–151°, lit.[6] m.p. 148–151°.

N,N-**Bis(2-hydroxy-1-naphthylmethyl)isopropylamine (IIe).**—The yield was 83%, m.p. 125–126°, after recrystallization from methanol–1-dimethylformamide (6:1).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.75. Found: C, 80.53; H, 6.95.

The **hydrochloride** melted at 163–164°, after recrystallization from methanol.

Anal. Calcd. for $C_{25}H_{26}ClNO_2$: Cl^-, 8.69. Found: Cl^-, 8.73.

Treatment of 1-*t*-Octylaminomethyl-2-naphthol (IIIg) with Hot Ethanol.—1-*t*-Octylaminomethyl-2-naphthol (2.5 g.) was warmed to 50–55° in 30 ml. of 95% ethanol for 5 min. and then kept at room temperature for 2 days. Removal of the solvents under reduced pressure gave an oil which was dissolved in 100 ml. of ether. The resulting solution was extracted with 100 ml. of water containing 2 g. of sodium hydroxide. The ether extract was washed with water and dried over sodium sulfate. Evaporation of the ether gave a solid, m.p. 78–80°. It was recrystallized from 95% ethanol to yield 0.45 g. (34%), m.p. 82–83°; mixture melting point with an authentic sample of 2-*t*-octyl-1*H*-2,3-dihydronaphth[1,2-*e*][1,3]oxazine, m.p. 83–84°, gave no depression.

The aqueous extracts were washed with ether. Upon adding 37% hydrochloric acid to pH 1, a white solid separated. It readily dissolved in ether. Removal of the ether gave 0.95 g. (73% yield) of bis(2-hydroxy-1-naphthyl)methane; melting point and mixture melting point with authentic specimen was 200–202°, lit.[12] m.p. 200°.

The aqueous extracts were neutralized with potassium bicarbonate and extracted with ether. Removal of the ether gave only a trace of oil.

N-**Cyclohexyl-*N*-(2-acetoxy-1-naphthylmethyl)acetamide.**—Acetic anhydride (10 g., 0.12 mole) was added to a solution of 4 g. of 1-cyclohexylaminomethyl-2-naphthol (0.016 mole) in 20 ml. of pyridine cooled on an ice bath. After 24 hr. at room temperature, 70 ml. of water was added. Upon cooling 4.8 g. (88% yield) of solid, m.p. 107–108°, separated. The product was recrystallized twice from methanol containing a trace of water, m.p. 108–109°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.32; H, 7.42. Found: C, 74.43; H, 7.37.

N-α-**Methylbenzyl-*N*-(2-acetoxy-1-naphthylmethyl)acetamide** was prepared from Mannich base by above procedure, 61% yield, m.p. 119–121°, from methanol.

Anal. Calcd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41. Found: C, 76.30; H, 7.00.

N-α-**Methylbenzyl-*N*-(2-hydroxy-1-naphthylmethyl)acetamide.**—Hydrolysis of the above ester in 2% potassium hydroxide in 95% ethanol at 25° for 3 hr. gave a product, m.p. 160–160.5°, after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.63. Found: C, 78.77; H, 6.59.

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Amine Exchange Reactions. Mannich Bases from Aromatic Amines[1]

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An exchange reaction occurs readily between tertiary Mannich bases (I) and primary and secondary arylamines, making accessible the monosubstituted arylamine Mannich bases (II and IV) in good yield. The arylamines used include polycyclic and heterocyclic bases as well as diamines. Experiments suggest that the overall amine-exchange reaction may proceed both by a substitution as well as by an elimination–addition mechanism.

A survey of the literature[2] concerning the Mannich reaction, using ketones as the acidic entity, reveals that, although the range of aliphatic amines used is virtually unlimited, the only reported successful condensation using an arylamine is the synthesis, in unstated yield, of 1,2,6-triphenyl-4-piperidone[3] from acetone, benzaldehyde, and aniline. Attempted Mannich reaction[4] between acetophenone, formaldehyde, and aniline hydrochloride failed to give the required β-anilinopropiophenone (IIa), leading instead to the formation of polymeric products derived from the aldehyde and amine.

Only a few isolated examples[5–9] of such condensations have appeared since that observation, and Mannich bases of type II are not readily available and cannot be prepared by the standard Mannich reaction. A number of syntheses of β-arylamino ketones (II) by other routes appear in the literature[10–12] but the methods are usually complex, the starting materials difficultly accessible, and the preparations confined to specific examples and not general in scope.

R–$COCH_2CH_2$–NR'_2	I	a	R = Ph; Ar = Ph
R–$COCH_2CH_2$–NHAr	II	b	R = Me; R′ = Et
R–$COCH_2CH_2$–NHR′	III	e	R = Me; Ar = Ph
		d	R = Ph; R′ = Et
R–$COCH_2CH_2$–NMeAr	IV	e	R = R′ = Me
Ph–$COCHMeCH_2NEt_2$	V	f	R = Ph; Ar = pClC_6H_4
Ph–$COCHMeCH_2NHC_6H_4$–*p*–Cl	VI	g	R = Ph; R′ = Me

It was shown recently[13] that the exchange reaction between tertiary Mannich bases (I) and primary alkyl-

(1) This work was partially supported by a grant (HE 5881) from the National Institutes of Health, U. S. Public Health Service.

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TABLE I

β-ARYLAMINOPROPIOPHENONES[a] $PhCOCH_2CH_2NHAr$

Ar	Reaction time, hr.	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	1	90	113–114					
p-MeC_6H_4	1	87	114–115	*b*				
p-$MeOC_6H_4$	1	89	111–112	*c*				
p-ClC_6H_4	1	88	134–135	*d*				
p-$C_6H_5COC_6H_4$	4	90	131–132	$C_{22}H_{19}NO_2$	80.26	80.22	5.91	5.81
p-$MeCOC_6H_4$	16	79	178–180	$C_{17}H_{17}NO_2$	76.38	76.21	6.41	6.50
p-$NO_2C_6H_4$	30	67	173–175	$C_{15}H_{14}N_2O_3$	66.65	66.48	5.22	5.39
p-$MeCONHC_6H_4$	12	80	144–145	$C_{17}H_{18}N_2O_2$	72.32	72.28	6.43	6.45
p-$HOOCC_6H_4$	1	84	210–211	$C_{16}H_{15}NO_3$	71.36	71.06	5.61	5.58
1-Pyrenyl	15	50	156–157	$C_{25}H_{19}NO$	85.93	85.72	5.48	5.54
2-Naphthyl	12	81	150–151	$C_{19}H_{17}NO$	82.87	82.71	6.23	6.42
2-Pyridyl	4	74	88–89	$C_{14}H_{14}N_2O$	74.30	74.27	6.24	6.19
3-Pyridyl	2	85	98–99	$C_{14}H_{14}N_2O$	74.30	73.99	6.24	6.27
3-Quinolyl	1	76	151–152	$C_{18}H_{16}N_2O$	78.23	77.96	5.84	5.83

[a] Prepared by method B. [b] Lit.[15] m.p. 113–114°. [c] Lit.[15] m.p. 114–115°. [d] Lit.[15] m.p. 136–138°.

amines gives the monosubstituted secondary Mannich bases (III), *e.g.*, reaction 1. Since Mannich bases from arylamines were required for other work, the application of this exchange reaction to aromatic amines was next investigated. We now report a method by which these compounds can be readily obtained in good yield.[14]

Equimolar quantities of the tertiary aliphatic Mannich base 1-diethylamino-3-butanone (Ib) and aniline hydrochloride reacted exothermally at room temperature; the mixture first became homogeneous, then crystals of diethylamine hydrochloride separated. The required 1-anilinobutan-3-one (IIc) was isolated in 70% yield. When the reactants were refluxed in 50% ethanol for a short time, the yield was increased to 86%. The reaction could be carried out using either the Mannich base and an arylamine salt, or the Mannich base hydrochloride and an arylamine, or a mixture of the two bases with the addition of a molar proportion of hydrochloric acid.

By this means the required 1-arylamino-3-butanones (II, R = Me) were prepared from a range of p-substituted anilines $RC_6H_4NH_2$ in which R = H, Me, OMe, Cl, and Ph, as well as with β-naphthylamine. The aromatic tertiary Mannich base β-diethylaminopropiophenone (Id) could be used under the same experimental conditions and readily underwent amine exchange with a variety of primary aromatic amines to give the β-arylaminopropiophenones (II, R = Ph) shown in Table I. The arylamines used include polycyclic and heterocyclic bases, as well as diamines. When methylaniline was employed as the arylamine moiety, amine exchange took place readily with both Ie and Ig to give, respectively, 1-(N-methylanilino)-3-butanone (IVc) and β-(N-methylanilino)propiophenone (IVa), both in 45% yield. The amine-exchange method, therefore, appears to be applicable to secondary arylamines also.

Since this work was completed, a recent publication[15] has appeared giving the preparation of several β-arylaminopropiophenones (IIa) in 37 to 62% yield by prolonged refluxing of β-dialkylaminopropiophenone hydrochloride and an aromatic primary amine. However, the results reported in the present study show that the reaction proceeds under milder conditions and has a wider range of applicability than was indicated by these authors.[15]

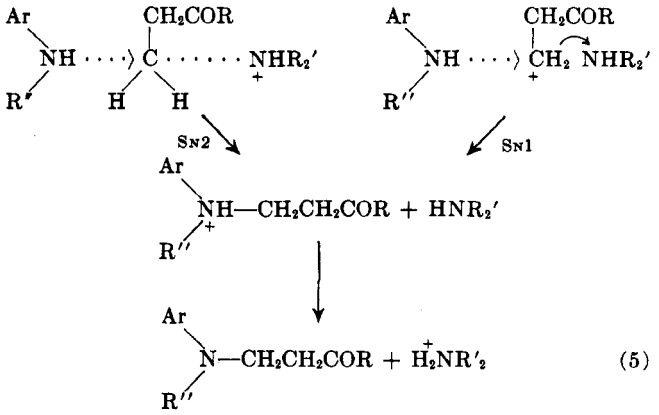
$$PhCOCH_2CH_2NEt_2 + C_6H_{11}NH_2 \longrightarrow PhCOCH_2CH_2NHC_6H_{11} + Et_2NH \quad (1)$$

$$RCOCH_2CH_2\overset{+}{N}HR_2' + ArNHR'' \longrightarrow RCOCH_2CH_2NR''Ar + R_2'\overset{+}{N}H_2 \quad (2)$$

$$RCOCH(H)CH_2\overset{+}{N}HR_2' \underset{3b}{\overset{3a}{\rightleftharpoons}} RCOCH{=}CH_2 + H_2\overset{+}{N}R_2' \quad (3)$$

$$RCOCH{=}CH_2 + Ar\,NHR'' \longrightarrow RCOCH_2CH_2NR''Ar \quad (4)$$

IV



(5)

Using aniline or methylaniline as the arylamine, the over-all amine exchange (eq. 2) may proceed either by an elimination reaction (eq. 3a) followed by a Michael addition (eq. 4) with the arylamine to give the product (IV) or alternatively by a direct substitution (reaction 5) which may be either concerted (SN2) or may occur *via* an intermediate carbonium ion (SN1) with identical results. Application of the amine exchange reaction to the branched-chain Mannich base β-diethylamino-α-methylpropiophenone (V) and p-chloroaniline resulted in a 20% yield of β-(p-chloroanilino)-α-methylpropiophenone (VI), compared with a 90% yield of the corresponding unbranched β-(p-chloroanilino)-propiophenone (IIf). If the N-deuterioarylamine were used, in the form of its deuteriochloride salt, and reaction (eq. 2) carried out in deuterium oxide as solvent,

(14) A preliminary publication has appeared in *Chem. Ind.* (London), 690 (1963).

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then (following the instantaneous proton transfer to the stronger base) the elimination–addition mechanism (reactions 3 and 4) would result in the incorporation of one atom of deuterium into the α-methylene group (C-2) in the products 1-anilino-3-butanone (IIc) and 1-(N-methylanilino)-3-butanone (IVc), while, if the direct substitution (reaction 5) operated, no deuterium due to this substitution reaction would appear in that position.

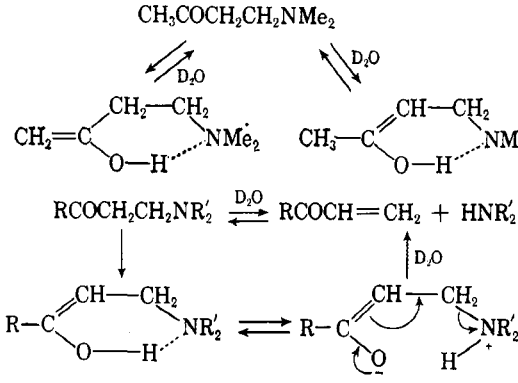
The use of n.m.r. spectroscopy offers a highly sensitive method for the location and estimation of deuterium substitution in a molecule.[16] To simplify the n.m.r. spectra, methylaniline was initially used as the arylamine and 1-dimethylamino-3-butanone (Ie) as the Mannich base.

In 1-dimethylamino-3-butanone, the methyl and dimethyl group appeared as singlets at δ 1.93 and 2.00 p.p.m., respectively, and the methylene groups as a multiplet at δ 2.36 p.p.m. In 1-(N-methylanilino)-3-butanone (IVc), the C-methyl and N-methyl singlets were found at δ 1.85 and 2.70 p.p.m., respectively, and the methylene groups as two separate triplets, δ 2.37 (C-2) and 3.47 (C-1) p.p.m. (shifted by the adjacent phenyl group), both with J = 7 c.p.s. The aromatic multiplet was at δ 6.94. The n.m.r. spectrum of 1-anilino-3-butanone (IIc) showed the methyl group and the aminohydrogen as singlets at δ 1.86 and 4.08 p.p.m., respectively, and the methylene groups as well-separated triplets, δ 2.39 (C-2) and 3.18 (C-1) p.p.m., with J = 7 c.p.s. in both cases. The aromatic multiplet was located at δ 6.95 p.p.m.

N-Deuteriomethylaniline and N-deuterioaniline deuteriochlorides were prepared by repeated treatment of the respective hydrochlorides with deuterium oxide until the infrared spectrum of the product showed no further change. Deuteration could be followed by a decrease in the absorption bands at 2920 and 2820 cm.$^{-1}$ ($\overset{+}{N}H_2$),[17] and a corresponding increase in bands at 2220 and 2120 cm.$^{-1}$ ($\overset{+}{N}D_2$).

Before carrying out the reaction using the deuterated arylamine salts, it was necessary to ascertain the extent of self-deuteration of 1-dimethylamino-3-butanone (Ie) under the reaction conditions used. It is well-known[18] that, *e.g.*, acetone undergoes rapid deuteration in the presence of alkali, but the occurrence of deuteration as a result of self-enolization under the sole influence of the basic group in the same molecule does not seem to have been observed previously.

When Ie alone was treated under the constant experimental conditions, the product was indeed found to contain, from the integrated n.m.r. spectrum, 1.66 and 2.27 D in positions 2 and 4, respectively, of 1-dimethylamino-3-butanone (Ie), the hydrogen content of the rest of the molecule being unchanged. The deuterium may be due to reversible self-enolization to the two enol forms stabilized by hydrogen bonding (reaction 6) and to some elimination–recombination (reaction 7); the figures found are in the ratio 2.28:3. Treatment of the deuteriochloride of Ie alone under the same condition gave a base (liberated at 0° using sodium ethoxide) which contained 1.22 and 1.60 D at positions 2 and 4; the rest of the molecule remained



unchanged. Although the total deuterium incorporation in the salt was less (as expected since the nitrogen was protonated), these figures are again in almost the same ratio 2.30:3. From the experimentally found deuterium content, the relative rates of deuterium exchange at C-2 and C-4 in Ie and its deuteriochloride may be calculated. In every experiment 15 moles of deuterium oxide per mole of Ie were used. Employing the following more accurate second-order equation

$$kt = \log \frac{a}{a - x} - \log \frac{b}{b - x}$$

which takes into account the change in the concentration of deuterium oxide during the time t, then for the base (Ie) at C-2, a = 2, b = 15, and x = 1.66, giving $(k_2)t$ = 0.7186. Similarly from C-4, a = 3, b = 15, and x = 2.27 gives $(k_4)t$ = 0.5425, and k_2/k_4 = 1.325. For the deuteriochloride of Ie, the same method of calculation yields $(k_2)t$ = 0.3720 and $(k_4)t$ = 0.2820, whence k_2/k_4 = 1.320. Thus, although the extent of deuteration in the salt is less, the ratio of the rates of deuteration at C-2 and C-4 is unchanged. It is clear that the rate of deuterium exchange in Ie is determined by the acid–base interaction (self-enolization, reaction 6) occurring initially as formation of a hydrogen bond and proceeding to a complete transfer of a proton and resultant ionization. In view of the very weak nature of, *e.g.*, acetone as an acid[19] in water (pK_a 20), this rate is surprisingly rapid.

Reaction of deuterioaniline deuteriochloride with Ie in deuterium oxide and isolation of the product (IIe) by extraction with anhydrous ether gave a material, the integrated n.m.r. spectrum of which showed incorporation of 1.7 D at C-2 and 2.2 D at C-4 in the 1-anilinobutan-3-one (IIc), as well as the expected deuteration of the amino group.

Since the nature of the amine exchange reaction as either elimination–addition or substitution can only affect the extent of deuteration at C-2 but not that at C-4, it is seen that, using the previously determined

(16) N.m.r. spectra were determined on the neat liquids at 60 Mc. using a Varian HR-60 instrument, with chemical shifts given in p.p.m. from a trace of dissolved tetramethylsilane. Deuterium content at the various molecular sites was determined from proton count data obtained using the electronic integrator. Each determination was the mean of five runs; the standard deviation of the average value was about 2%.

(17) P. J. Stone, J. C. Craig, and H. W. Thompson, *J. Chem. Soc.*, 52 (1958).

(18) (a) K. F. Bonhöffer, K. H. Geib, and O. Reitz, *J. Chem. Phys.*, **7**, 664 (1939); (b) S. K. Hsu, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938); C. L. Wilson, *ibid.*, 1550 (1936).

(19) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

ratio[20a] $k_2/k_4 = 1.32$ and the figure of 2.2 D (found) at C-4 in the product (IIc), the calculated amount of deuteration (x) at C-2 in IIc due to the self-enolization may be found from the expression that follows

$$\frac{k_2}{k_4} = 1.32 = \frac{\log \frac{2}{2-x} - \log \frac{15}{15-x}}{\log \frac{3}{3-2.2} - \log \frac{15}{15-2.2}}$$

whence $x = 1.61$ D. The experimentally found deuterium content at C-2 is 1.7 D, and it appears that only very little additional deuterium is present at C-2, suggesting that the amine exchange reaction occurs substantially (90%) as substitution (reaction 5) and only to an extent of 10% as elimination–addition (reactions 3 and 4) in the case of aniline as the arylamine, since the substitution mechanism would contribute no deuterium at C-2, while the elimination–addition would introduce one deuterium into that position.

When the reaction was repeated using deuteriomethylaniline deuteriochloride and Ie in deuterium oxide, the product (IVc) was found to contain 1.36 D at C-2 and 1.30 D at C-4. Using the same calculation as before, the ratio $k_2/k_4 = 1.32$ and the figure 1.30 D at C-4 gives 1.01 D as the calculated amount of deuteration expected at C-2 due to self-enolization.[20b] The value found (1.36 D) thus represents a substantial proportion (up to *ca.* 35%) of the elimination–addition, with a corresponding reduction in the substitution pathway to *ca.* 65%. Since methylaniline reacts more slowly than aniline in the over-all amine-exchange reaction, it might be expected that the product (IVc) from methylaniline would contain more deuterium than the product (IIc) from aniline, due to the greater possibility for deuteration of the molecules of aliphatic Mannich base (Ie) by reactions 3, 6, and 7, *before* they undergo reaction 2. However, the total deuterium content of IVc at C-2 and C-4 was only 2.66 D compared with 3.9 D for IIc at the same positions.

The unexpectedly large amount of deuteration at C-2 and C-4 in the product (IIc) from aniline may be due to the small, but significant, water solubility of this product (IIc), resulting in some deuterium–hydrogen exchange by reaction 6 in both the C-2 and C-4 positions *after* the formation of IIc. This should not occur in the case of the product (IVc) which is substantially insoluble in water. This hypothesis was checked by submitting both IIc and IVc to deuterium oxide under the exact conditions of the amine-exchange reaction, followed by removal of the heavy water *in vacuo* when it was found that there was indeed no detectable deuterium in the recovered 1-(N-methylanilino)-3-butanone (IVc), while the recovered 1-anilino-3-butanone (IIc) showed (apart from complete deuteration of the NH group) incorporation of 0.41 D at C-2 and 0.53 D at C-4. The increased amount of deuterium in IIc is thus explicable.

(20) (a) If the ratio found for the self-deuteration of IIc, $k_2/k_4 = 1.28$ (following), is used for this calculation, then $x = 1.59$ D, *i.e.*, not significantly different from the above. (b) If pseudounimolecular kinetics[19c] are employed as a first approximation in view of the large molar excess of deuterium oxide used, the simplified expression $kt = \log a/a - x$ gives $k_2/k_4 = 1.25$ and 1.24 for Ie and its deuteriochloride, respectively, and thence the values $x = 1.61$ D for IIc and $x = 1.01$ D for IVc, *i.e.*, identical with those obtained by the more exact bimolecular equation. (c) A. I. Shatenshtein, "Isotopic Exchange and the Replacement of Hydrogen in Organic Compounds," Consultants Bureau, New York, N. Y., 1962, p. 23.

It is interesting that the ratio k_2/k_4 for the deuterium incorporation in IIc, calculated as before in the case of Ie, gives $k_2/k_4 = 1.28$ for IIc. The arylamine Mannich bases of type IIa and IVa showed greatly enhanced stability. They have been found to be stable to heat, even distilling unchanged at temperatures up to 200° *in vacuo*, *i.e.*, under conditions in which any incipient fragmentation would readily go to completion as it does in the case of their aliphatic analogs. This increased stability is presumably due to their low basic strength (pK_a *ca.* 4.5) and the resultant decrease in reactions 6 and 7.

When methylaniline was refluxed with the tertiary Mannich base (Ig) in 50% aqueous alcohol under the previous conditions, but in the *absence of acid*, the product (IVa) was obtained in reduced (31%) yield. Since the dimethylamino moiety is a poor leaving group, this would indicate that, under these conditions, elimination–addition predominates. In order to test the speed of the addition reaction itself, phenyl vinyl ketone was treated with either dimethylamine or its hydrochloride and afforded 85% of Ig after 5 min. in each case. The same ketone when treated with methylaniline gave 57% of the product (IVa) in that time, or 66% after 2 hr.

The finding that the yield of IVa (45%) from the over-all exchange reaction of methylaniline hydrochloride and Ig after 2 hr. is not further increased by extending the reaction time to 5 hr. indicates the existence of an equilibrium, as does the fact that equimolar amounts of phenyl vinyl ketone, methylaniline, and dimethylamine hydrochloride gave an identical yield (44%) of IVa after 2 hr.

A possible interpretation of these results would be that the exchange reaction (5) occurs, probably by an SN1 mechanism in the highly polar medium employed, to give IVa and dimethylamine hydrochloride which accumulates. At the same time, reaction 3 also is taking place, forming the vinyl ketone and more dimethylamine salt. Initially some vinyl ketone reacts by addition with the arylamine present, but, as more and more dimethylamine salt is produced, this will compete increasingly with the methylaniline for any vinyl ketone formed, and thus reaction 3b will be promoted at the expense of reaction 4. After 2 hr., this equilibrium appears to be entirely in favor of reaction 3b.

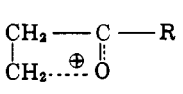
With the equimolar amounts of phenyl vinyl ketone, methylaniline, and dimethylamine hydrochloride, no SN1 reaction can occur until reaction 3b has produced some Ig hydrochloride. Since reaction 3b is faster than reaction 4, only a small amount of addition will take place in that time, after which the SN1 reaction will give the same (44%) yield of IVa.

Using the Mannich base (Ig) and methylaniline only, no proton is present to turn the dimethylamino moiety into a leaving group, and reaction 5 cannot take place. Only reactions 6 and 7 occur, and only the latter produces vinyl ketone and dimethylamine. Since no dimethylamine salt is formed from reaction 5, reaction 4 will be promoted and reaction 3 retarded by the presence of a molar amount of methylaniline, resulting in a higher (31%) yield of IVa by addition compared with that (*ca.* one-third of 44% total yield) obtained previously.

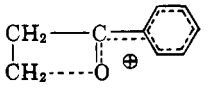
Using aniline as the arylamine, the SN1 reaction ap-

pears to predominate and to be markedly faster than with methylaniline (86% yield as against 45% under the same conditions). The reason may well be steric, since it is known that nucleophilic attack on carbon is usually more subject to steric hindrance than is coordination with a proton,[21] and this steric effect may destroy the usual correlation between the rate of nucleophilic substitution and the basicity of the reagent.

It is possible that the facile SN1 process represented by the over-all reaction 2 is dependent upon, and substantially promoted by, powerful neighboring group assistance from the carbonyl function in I and by the formation of the resonating bridged carbonium–oxonium ion (VII). The presence of R = C_6H_5 would



VII



VIII

further assist in dispersing the positive charge and thereby aid in the formation of the bridged ion (VIII). This type of anchimeric assistance may account for the numerous cases of amine exchange observed to occur in Mannich bases.[22]

Experimental

1-Anilino-3-butanone (IIc). A.—Thirteen grams (0.10 mole) of aniline hydrochloride and 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone were mixed at room temperature. The reaction was exothermic and initially became homogeneous, then large leaflets separated after *ca.* 30 min. The mixture was kept overnight at room temperature, then distributed between ether and water. Distillation of the dried (sodium sulfate) ether layer gave a small forerun of unchanged aniline, then 11.3 g. (70%) of 1-anilino-3-butanone, b.p. 100–102° (0.25 mm.), $n^{17}D$ 1.5640, m.p. 34–36°. The semicarbazone crystallized from ethanol as needles, m.p. 165–166°; lit.[11] b.p. 138–148° (7 mm.), $n^{20}D$ 1.5615, m.p. 35–36° for the ketone and m.p. 166° for the semicarbazone.

B.—A solution of 13.0 g. (0.10 mole) of aniline hydrochloride and 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone in 50 ml. of ethanol and 50 ml. of water was heated under reflux for 1 hr. The solvent was removed *in vacuo;* then the reaction worked up as in A. The product was 13.9 g. (86%) of 1-anilino-3-butanone, identical with that obtained in A.

1-(*p*-Anisidino)-3-butanone.—A mixture of 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone, 12.3 g. (0.10 mole) of *p*-anisidine, 10 ml. of 10 *N* hydrochloric acid, 50 ml. of ethanol, and 50 ml. of water was heated under reflux for 1 hr. The solvent was evaporated *in vacuo;* the residue was distributed between ether and water. Distillation of the dried (sodium sulfate) ether layer gave 16.2 g. (84%) of 1-*p*-anisidino-3-butanone, b.p. 128–130° (0.1 mm.), $n^{16}D$ 1.5603.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.01; H, 7.88.

The semicarbazone crystallized from ethanol as needles, m.p. 151–152°, lit.[12] m.p. 151°.

1-(*p*-Toluidino)-3-butanone.—A mixture of 14.4 g. (0.10 mole) of *p*-toluidine hydrochloride, 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone, 50 ml. of ethanol, and 50 ml. of water was treated as in B. The product was 14.0 g. (80%) of 1-(*p*-toluidino)-3-butanone, b.p. 118–120° (1.0 mm.), m.p. 42–43°. The semicarbazone crystallized from ethanol as needles, m.p. 162–164°; lit.[12] m.p. 41–43° for the ketone and m.p. 163° for the semicarbazone.

1-(*p*-Chloroanilino)-3-butanone.—A mixture of 7.2 g. (0.05 mole) of 1-diethylamino-3-butanone, 8.3 g. (0.05 mole) of *p*-chloroaniline hydrochloride, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. On cooling, the product was filtered and crystallized from methanol, giving 7.8 g. (77%) of 1-(*p*-chloroanilino)-3-butanone, m.p. 74–75°.

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.74; H, 6.12. Found: C, 60.66; H, 5.98.

The semicarbazone crystallized from ethanol as needles, m.p. 173–174°.

Anal. Calcd. for $C_{11}H_{15}ClN_4O$: C, 51.87; H, 5.94. Found: C, 51.60; H, 5.76.

1-(β-Naphthylamino)-3-butanone.—A mixture of 9.0 g. (0.05 mole) of β-naphthylamine, 7.15 g. (0.05 mole) of 1-diethylamino-3-butanone, 5 ml. of 10 *N* hydrochloric acid, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. On cooling, the product was collected by filtration. Crystallization from methanol gave 8.2 g. (76%) of 1-(β-naphthylamino)-3-butanone, m.p. 72–74°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.82; H, 7.10. Found: C, 78.61; H, 7.15.

1-(4′-Phenylanilino)-3-butanone.—A mixture of 7.2 g. (0.05 mole) of 1-diethylamino-3-butanone, 10.3 g. (0.05 mole) of 4-phenylaniline hydrochloride, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 4 hr. On cooling, the product was filtered and crystallized from methanol. The product was 9.9 g. (82%) of 1-(4′-phenylanilino)-3-butanone, m.p. 87–88°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.02; H, 6.99.

β-Anilinopropiophenone (IIa). Method A.—A mixture of 6.5 g. (0.05 mole) of aniline hydrochloride and 10.3 g. (0.05 mole) of β-diethylaminopropiophenone was kept overnight at room temperature. Initially, an exothermic reaction set in, the mixture became homogeneous, then set to a crystalline mass. Water was added and the product was isolated with chloroform. Evaporation of the dried (sodium sulfate) chloroform extract and crystallization from ethanol gave 8.5 g. (75%) of β-anilinopropiophenone, m.p. 113–114°, lit.[23] m.p. 111–112°.

Method B.—A mixture of 4.7 g. (0.05 mole) of aniline, 10.3 g. (0.05 mole) of β-diethylaminopropiophenone, 25 ml. of ethanol, 25 ml. of water, and 5 ml. of 10 *N* hydrochloric acid was heated under reflux. A solid separated after a few minutes, and after 1 hr. the mixture was cooled and the product was filtered. Crystallization from ethanol gave 10.1 g. (90%) of β-anilinopropiophenone, m.p. and m.m.p. 113–114°.

β-(*p*-Chloroanilino)-α-methylpropiophenone (VI).—A mixture of 8.2 g. (0.05 mole) of *p*-chloroaniline hydrochloride, 11.0 g. (0.05 mole) of β-diethylamino-α-methylpropiophenone, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The solvent was evaporated *in vacuo,* water was added, and the product was isolated with ether. Distillation gave 4.1 g. (64%) of unchanged *p*-chloroaniline, b.p. 85–90° (0.1 mm.), m.p. and m.m.p. 73–75°. Crystallization of the residue from petroleum ether (b.p. 60–90°) gave 2.6 g. (20%) of β-(*p*-chloroanilino)-α-methylpropiophenone as plates, m.p. 70–71°.

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89. Found: C, 70.18; H, 5.82.

N,N′-Bis(β-benzoylethyl)-*o*-phenylenediamine.—A mixture of 5.4 g. (0.05 mole) of *o*-phenylenediamine, 12.1 g. (0.05 mole) of β-diethylaminopropiophenone hydrochloride, and 50 ml. of ethanol was heated under reflux for 1 hr. On cooling, the product was filtered, taken up in benzene, and percolated through a short column of neutral alumina. Crystallization from ethanol gave 7.8 g. (42%) of N,N′-bis(β-benzoylethyl)-*o*-phenylenediamine as needles, m.p. 139–140°.

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.40; H, 6.49. Found: C, 77.55; H, 6.62.

N,N′-Bis(β-benzoylethyl)-*p*-phenylenediamine.—A mixture of 5.4 g. (0.05 mole) of *p*-phenylenediamine, 12.1 g. (0.05 mole) of β-diethylaminopropiophenone hydrochloride, and 50 ml. of ethanol was heated under reflux for 1 hr. under nitrogen. Crystallization (charcoal) of the product from chloroform gave 14 g. (76%) of buff leaflets, m.p. 179–181°.

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.40; H, 6.49; N, 7.52. Found: C, 76.95; H, 6.41; N, 7.32.

1-(N-Methylanilino)-3-butanone (IVc). A.—A mixture of 10.7 g. (0.10 mole) of N-methylaniline, 15.2 g. (0.10 mole) of 1-dimethylamino-3-butanone hydrochloride, 50 ml. of ethanol, and 50 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo,* water was added, and the product was isolated with ether. Distillation of the dried (sodium sulfate)

(21) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 159.

(22) J. H. Brewster and E. L. Eliel, "Organic Reactions," Coll. Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 138.

(23) J. Kenner and F. S. Statham, *J. Chem. Soc.*, 299 (1935).

ether extract gave unchanged N-methylaniline, then 7.6 g. (43%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}D$ 1.5495.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.39; H, 8.67.

The semicarbazone crystallized from ethanol as needles, m.p. 169–171°; lit.[12] b.p. 153–161° (14 mm.) for the ketone and m.p. 163° for the semicarbazone.

Anal. Calcd. for $C_{12}H_{18}N_4O$: C, 61.51; H, 7.74. Found: C, 61.31; H, 7.41.

B.—A mixture of 10.7 g. (0.10 mole) of N-methylaniline, 15.2 g. (0.10 mole) of 1-dimethylamino-3-butanone hydrochloride, and 30 ml. of water was heated on the steam bath for 2 hr., and then worked up as in A. The product was 5.1 g. (30%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}D$ 1.5495.

Deuterated 1-(N-Methylanilino)-3-butanone.—A solution of 4.3 g. (0.03 mole) of N-methylaniline hydrochloride in 6 ml. of deuterium oxide was evaporated to dryness *in vacuo* at 25°. This procedure was repeated six times, after which a constant infrared spectrum was obtained. The deuterated salt was heated on the steam bath for 2 hr. with 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide; then the cooled reaction mixture was extracted with anhydrous ether. Distillation of the ether extract gave a forerun of deuterated N-methylaniline then deuterated 1-(N-methylanilino)-3-butanone, b.p. 81–82° (0.1 mm.), $n^{24}D$ 1.5475.

Deuterated 1-Anilino-3-butanone.—Treatment of 4.0 g. (0.03 mole) of aniline hydrochloride as above gave deuterated 1-anilino-3-butanone, b.p. 94–95° (2 mm.), $n^{24}D$ 1.5530.

Self-Deuteration of 1-Dimethylamino-3-butanone.—A mixture of 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide was heated on the steam bath for 2 hr., and then the cooled mixture was extracted with anhydrous ether. Distillation of the ether gave deuterated 1-dimethylamino-3-butanone, b.p. 60–62° (25 mm.), $n^{25}D$ 1.4425.

β-(N-Methylanilino)propiophenone (IVa). A.—A mixture of 3.21 g. (0.03 mole) of N-methylaniline, 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, the residue was distributed between ether and water, and the dried (sodium sulfate) ether layer was evaporated finally at 100° (1.0 mm.) Crystallization of the residue from ethanol gave 3.2 g. (45%) of β-(N-methylanilino)-propiophenone as needles, m.p. 60–61°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.41; H, 6.86.

B.—An ice-cold solution of 1.5 g. of sodium hydroxide in 50 ml. of water was added to 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, and the liberated base was extracted with ether. The ether was washed with water, dried (sodium sulfate), and evaporated. The resulting β-dimethylaminopropiophenone was heated under reflux for 2 hr. with 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water; then the solvent was evaporated *in vacuo*. The residue was taken up in 75 ml. of ice-cold 1 *N* hydrochloric acid, the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were isolated with ether; the ether was dried (sodium sulfate) and evaporated finally at 100° (1.0 mm.). Crystallization of the residue from ethanol gave 2.2 g. (31%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

C.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, water was added, and the product was isolated with ether. Evaporation of the dried (sodium sulfate) ether extracts finally at 100° (1.0 mm.) and crystallization of the residue from ethanol gave 3.1 g. (43%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

D.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr., and then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of 1 *N* hydrochloric acid; the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were extracted with ether and the dried (sodium sulfate) ether extracts were evaporated finally at 100° (1 mm.). Crystallization of the residue from ethanol gave 4.7 g. (66%) of β-(N-methylanilino)-propiophenone, m.p. and m.m.p. 60–61°.

E.—The same reactants were heated for 5 min. then worked up as before. The product was 4.1 g. (57%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

β-Dimethylaminopropiophenone (Ig). A.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 1.35 g. (0.03 mole) of dimethylamine, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of ice-cold 1 *N* hydrochloric acid; the solution was washed with ether and then was brought to pH 14 with ice-cold 3 *N* sodium hydroxide. The product, isolated with ether, was 4.6 g. (86%) of β-dimethylaminopropiophenone, $n^{25}D$ 1.5240, m.p. 30–32°.

B.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was distributed between ether and ice–water, and the aqueous layer was made basic with ice-cold 3 *N* sodium hydroxide. Isolation with ether gave 4.4 g. (84%) of β-dimethylaminopropiophenone, identical with that obtained in A.

Isomerism in the Direct Chlorination of 2-Methylpyrazine[1a]

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The product of the direct chlorination of 2-methylpyrazine is shown to be a mixture of 2-chloro-3-methylpyrazine and 2-chloro-6-methylpyrazine.

The direct nuclear chlorination of alkylpyrazines recently reported[2,3] has greatly expedited the study of the pyrazine ring system. The alkylchloropyrazines obtained by this method are also available, though less conveniently, by the chlorination of the corresponding alkylhydroxypyrazines with a phosphorus halide. The alkylhydroxypyrazines are obtained *via* the condensation of amino acid amides with α-dicarbonyl compounds.[4] The commercial availability of the three alkylchloropyrazines Ia–c[5] prompted us to prepare a number of dialkylamino derivatives and related compounds for exploratory pharmacological screening.

When commercial Ia was treated with excess piperidine either alone or in the presence of aqueous base the product was shown by gas–liquid chromatography

(1) (a) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963; (b) Chemistry Department, Manchester College, North Manchester, Ind.

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(3) A. Hirschberg and P. E. Spoerri, *ibid.*, **26**, 2356 (1961); see also R. A. Pages and P. E. Spoerri, *ibid.*, **28**, 1702 (1963).

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).

(5) These compounds were generously supplied by the Wyandotte Chemicals Corp., the method of preparation being as described in ref. 1.