tration. The filtrate was concentrated *in vacuo* and passed through a Dowex-50 resin column in acid cycle. The eluate was evaporated to dryness and the residue recrystallized from about 20 ml. of concentrated nitric acid. Paper chromatography using ether–acetic acid–water; 13:3:1 as solvent showed only a single spot at this point.

The combined acids from several oxidations (0.25 g.) were dissolved in 10 ml. of anhydrous methanol and treated with an excess of ethereal diazomethane. Excess diazomethane was destroyed with acetic acid and the polymethylene removed by filtration. The solution was evaporated to dryness and the residue recrystallized from aqueous methanol. Further recrystallization from benzene–hexane gave an ester, m.p. 142–144°. This ester has been reported[18] to melt at 143–144°. An authentic sample[19] did not depress the melting point of the ester so prepared.

Tetramethyl Benzene-1,2,3,4-tetracarboxylate.—Oxidation of 1,2,3,4-tetraethylbenzene followed by esterification as described above gave the desired ester, m.p. 130–131°, which did not depress the melting point of an authentic sample prepared according to the method of Read and Purves.[19] These authors report that the ester melts at 130–131°.

Determination of Radioactivity.—Radioactivity was assessed with a Packard Tri-Carb scintillation counter Model 314 using a scintillation solution containing 2.5005 g. of PPO and 0.0182 g. of POPOP in 250 ml. of toluene solution. The counting efficiency was determined by the internal standard method, and counting was carried out a sufficient time so that the standard deviation did exceed 1%. An HVT setting of 950 v. and window settings were adjusted to give a maximum for $\frac{\text{effic.}^2}{\text{background}}$. The data in Table I were obtained.

(18) D. E. Read and C. B. Purves, *J. Am. Chem. Soc.*, **74**, 116 (1952).

(19) This authentic sample was prepared from 1,2,4,5-benzenetetracarboxylic acid kindly supplied by Dr. L. I. Smith.

Grignard Reagents from *o*-Bromobenzylamines[1]

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Magnesium metal has been found to react with *o*-bromobenzylamines to form organomagnesium compounds which behave like Grignard reagents. These have been treated with aldehydes, ketones, esters, etc., to give the expected products in excellent yields.

Ehrlich[2] has shown that *p*-bromodimethylaniline in absolute ether could react with magnesium if initially activated by ethyl bromide. Subsequently, this method was employed by several other investigators,[3] but only with *p*-bromodimethylaniline. The carbonation reaction on the Grignard reagent from *o*-bromodimethylaniline studied by Holmberg[3f] gave a symmetrical ketone.

Recently, Miescher and Marxer[4] have patented a procedure for preparing aminocarbinols from Grignard reagents of halogenoaliphatic tertiary amines of the type $R_2N(CH_2)_nX$ where $n \geq 3$. The reaction has to be initiated by traces of ethyl bromide and is completed in the presence of ketone or aldehyde.

The formation of organomagnesium compounds of the Grignard reagent type from haloaralkyl bases does not appear to have been previously reported. Such reagents could render possible syntheses of compounds otherwise not easily accessible.[5]

Some pecularities of Grignard reagents containing tertiary amino groups might be anticipated. Barrett[6] treated aromatic Grignard reagents with ω-dialkylaminocarboxylic esters having three or more methylene groups between the amino and the ester functions and obtained the bulk of their product as ketones despite the presence of large excess of the Grignard reagent. This observation suggests stabilization of the primary reaction adduct through coordination of metal with the unshared electrons of the nitrogen.

Magnesium metal reacts with *o*-bromobenzylamines of the type I to yield the desired organomagnesium derivatives II, soluble in anhydrous ether. These respond to the Gilman test[7] with Michler's ketone and give the normal reactions of Grignard reagents with aldehydes, ketones, esters, acid chlorides, isocyanates, and isothiocyanates. In such reactions the expected products were isolated in 50–70% yields. Analytical (iodimetric)[8a] assay of solutions of Grignard reagent

(1) Presented before the Division of Organic Chemistry at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 1961, p. 34-G.

(2) P. Ehrlich and F. Sachs, *Ber.*, **36**, 4296 (1903). This complex with Michler's ketone gives methyl violet—a well known lecture demonstration experiment.

(3) (a) F. Sachs and L. Sachs, *ibid.*, **37**, 3088 (1904); (b) S. S. Jenkins, *J. Am. Chem. Soc.*, **53**, 3115 (1931); (c) J. S. Chamberlain and M. F. Dull, *ibid.*, **50**, 3088 (1928); (d) H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940); (e) H. Gilman and R. H. Kirby, *ibid.*, **63**, 2046 (1941); (f) G. A. Holmberg, *Acta Chem. Scand.*, **9**, 555 (1955).

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

(5) After the completion of this work, F. N. Jones and C. H. Hauser [*J. Org. Chem.*, **27**, 701 (1962)] reported syntheses of a parallel nature using lithium reagents.

(6) P. A. Barrett, U. S. Patent 2,649,444 (August 18, 1953); *cf.* also British Patent 614,567 (December 17, 1948).

(7) The Gilman test was performed on the filtered ethereal solution of the Grignard complex. Traces of magnesium in acetic acid impart a greenish blue tint to the aqueous solution and can be misleading.

(8) (a) O. Job and R. Reich, *Bull. soc. chim.*, **33**, [4], 1414 (1923); *ibid.*, **37**, [4], 976 (1925); (b) The formation of a strained planar ring through the complex Mg ← N for the Grignard reagent from *o*-bromodimethylaniline has been suggested by Holmberg.[3f] High resolution n.m.r. studies are being made by Dr. B. Shapiro, Mellon Institute, Pittsburgh, Pa.

TABLE I

o-BROMOBENZYLAMINES

Compound	NRR′	Yield, %	Bases: B.p./pr.[a] m.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Salts: M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$N(CH_3)_2$[b,c]	63	41/6 μ	$C_9H_{12}BrN$	50.4	50.2	5.6	5.8	222	$C_9H_{12}BrN\cdot HCl$	43.1	43.4	5.2	5.1
2	$N(CH_2)_4$[b,d,e]	92	95/1 mm.	$C_{11}H_{14}BrN$	55.0	55.2	5.8	5.5	164	$C_{11}H_{14}BrN\cdot HCl$	47.8	47.6	5.4	5.5
3	$N(CH_2)_4O$[f,g]	98	102/80 μ	$C_{11}H_{14}BrNO$	51.6	51.4	5.5	5.3	224	$C_{11}H_{14}BrNO\cdot HCl$	45.1	45.3	5.2	5.5
4	$N(C_2H_5)_2$	88	65/40 μ	$C_{11}H_{16}BrN$	54.6	54.3	6.6	6.3	134–135	$C_{11}H_{16}BrN\cdot HCl$	47.4	47.6	6.1	6.3
5	$N(CH_2)_5$[h]	94	72/20 μ	$C_{12}H_{16}BrN$	56.7	56.7	6.3	6.2	245	$C_{12}H_{16}BrN\cdot HCl$	49.6	49.4	5.8	5.9
6	$N(CH_2)_4NCH_3$[b,i]	85	35	$C_{12}H_{17}BrN_2$	53.6	53.7	6.3	6.5	240	$C_{12}H_{17}BrN_2\cdot 2HCl$	42.1	42.2	5.5	5.7
7	$N(CH_3)C_6H_{11}$[j]	96	109/175 μ	$C_{14}H_{20}BrN$	59.6	59.8	7.1	7.3	186	$C_{14}H_{20}BrN\cdot HCl$	52.8	52.8	6.6	6.2
8	$N(CH_2)C_6H_{11}$[j]	99							178	$C_{14}H_{20}BrN\cdot CH_3I$[k]	42.5	42.5	5.4	5.4

[a] Boiling points for high vacuum distillations are actually furnace temperatures (*cf.* ref. 15). [b] J. W. Billinghurst and F. C. Copp, private communication. [c] Quaternary by-product was formed $(2\text{-}BrC_6H_4)_2N(CH_3)_2Br^-$, m.p. 181°. *Anal.* Calcd. for $C_{18}H_{18}Br_3N$: C, 41.5; H, 3.9. Found: C, 41.7; H, 3.9. [d] Pyrrolidino. [e] Quaternary by-product was formed $(2\text{-}BrC_6H_4)_2N(CH_2)_4Br^-$, m.p. 159°. *Anal.* Calcd. for $C_{18}H_{20}Br_3N$: C, 44.1; H, 4.1. Found: C, 43.9; H, 3.8. [f] Morpholino. [g] M. T. Leffler and E. H. Volwiler, *J. Am. Chem. Soc.*, **60**, 896 (1938). [h] Piperidino. [i] 4-Methyl-1-piperazinyl. [j] Methylcyclohexylamino. [k] Nitrogen. Calcd.: 3.31. Found: 3.30.

I II

indicated conversion of ArBr to ArMgBr in 87–90% yields. The actual nature of the reagent is still under study. Attempts to prepare analogous reagents from *m*- or *p*-bromobenzyl tertiary amines have so far been unsuccessful. For this reason and on general principles one is led to suspect participation of the amino nitrogen in the Grignard complex in place of one of the ether oxygens normally so involved. The forms IIIa–c would appear possible.[8b] Attempts at differentiation by dioxane precipitation[9] were inconclusive since nearly all the active material was precipitated.

Since any of the variants of III could have unusual solubilities, interpretations are even more doubtful than those formulated previously for such operations.

The amine moieties investigated (Table I) have been dimethylamino, diethylamino, methylcyclohexylamino, pyrrolidino, piperidino, morpholino, and 4 - methyl - 1 - piperazinyl. The latter two variants appear unsuitable in that no organomagnesium derivatives were formed. However, this point requires further investigation[10] as does the effect of increasing the number of carbon atoms between the amino group and the ring.

The carbonation reaction on the Grignard reagent from *o*-bromobenzylpiperidine was also studied. Since the substituted aminobenzoic acid formed would be difficult to isolate, the product was directly converted to the methiodide of the corresponding methyl ester in excellent yield.

That the aminocarbinols obtained in these reactions had *ortho* substitution retained from their starting compounds, *o*-bromobenzylamines, was established through cyclization[11] of the prod-

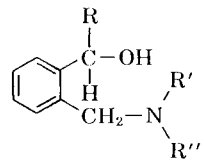
(9) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 102–103.

(10) It has been shown by Gilman and Swiss[3d] that Grignard reagents otherwise obtained with difficulty could be prepared indirectly through the reactions of the corresponding lithium compound with magnesium iodide.

(11) *Cf.* R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, **27**, 213 (1962).

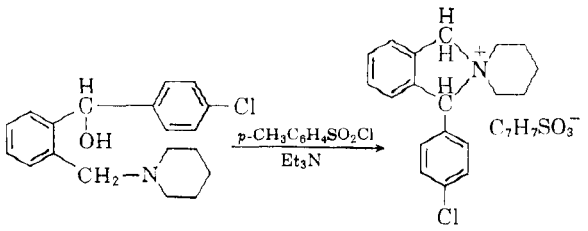
TABLE II

o-(SUBSTITUTED AMINOMETHYL)BENZHYDROLS



Compound	NR′R″	R	Bases: Yield, %	B.p./pr.[a] m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Salts: M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
9	$(CH_3)_2N$	C_6H_5[b]	90							198–199	$C_{16}H_{19}NO\cdot HCl$	69.2	69.3	7.2	6.9
10	$(CH_3)_2N$	2,5-$(CH_3O)_2C_6H_3$	46	87	$C_{18}H_{23}NO_3$	71.7	71.4	7.6	7.6	189	$C_{18}H_{23}NO_3\cdot HCl$	64.1	64.2	7.1	7.2
11	$(CH_3)_2N$	3,4,5-$(CH_3O)_3C_6H_2$	56	99	$C_{19}H_{25}NO_4$	68.8	69.1	7.5	7.5	210–211	$C_{19}H_{25}NO_4\cdot HCl$	62.0	61.8	7.1	7.4
12	$(CH_3)_2N$	2,5-$(C_2H_5O)_2C_6H_3$	95	74–75	$C_{20}H_{27}NO_3$	72.9	73.0	8.2	8.1	190–191	$C_{20}H_{27}NO_3\cdot HCl$	65.6	65.6	7.7	7.6
13	$(C_2H_5)_2N$	2,5-$(CH_3O)_2C_6H_3$	80	103	$C_{20}H_{27}NO_3$	72.9	72.6	8.2	8.1	183–184 (eff.)	$C_{20}H_{27}NO_3\cdot HCl\ 1/2H_2O$	64.1	64.5	7.7	7.7
14	$(C_2H_5)_2N$	2,5-$(C_2H_5O)_2C_6H_3$	70	76	$C_{22}H_{31}NO_3$	74.0	73.8	8.7	8.4	197–198	$C_{22}H_{31}NO_3\cdot HCl$	67.1	67.0	8.1	8.0
15	$(C_2H_5)_2N$	2,5-$(C_2H_5O)_2C_6H_3$								184	$C_{22}H_{31}NO_3\cdot CH_3I$	55.3	55.1	6.8	6.7
16	$(CH_2)_4N$[c]	3,4,5-$(CH_3O)_3C_6H_2$	59	143–144	$C_{21}H_{27}NO_4$	70.6	70.2	7.5	7.6	212–213	$C_{21}H_{27}NO_4\cdot HCl$	64.2	64.1	7.1	7.3
17	$(CH_2)_5N$[d]	C_6H_5	78	168–70/1 μ	$C_{19}H_{23}NO$	81.1	81.0	8.2	8.0	186–187	$C_{19}H_{23}NO\cdot HCl$	71.8	71.7	7.5	7.4
18	$(CH_2)_5N$[d]	4-ClC_6H_4	75	140–2/5 μ	$C_{19}H_{22}ClNO$	72.3	72.5	6.9	7.0	120–122 (eff.)	$C_{19}H_{22}ClNO\cdot HCl\cdot 1/2H_2O$	63.2	63.6	6.6	6.6
19	$(CH_2)_5N$[d]	4-ClC_6H_4								181–182	$C_{19}H_{22}ClNO\cdot CH_3I$	52.5	52.7	5.5	5.2
20	$(CH_2)_5N$[d]	3,4,5-$(CH_3O)_3C_6H_2$	51							183	$C_{22}H_{29}NO_4\cdot HCl$	64.9	64.7	7.4	7.5

[a] Footnote (*a*) Table I. [b] The base m.p. 70–71° has been reported by H. W. Bersch and R. Meyer, *Arch. Pharm.*, **287**, 613 (1954), prepared by the reaction of 2-dimethylaminomethylbenzaldehyde and phenylmagnesium bromide. Nitrogen analyses of salts. Compound 13, calcd.: 3.7. Found: 3.7. Compound 14, calcd.: 3.5. Found: 3.2. Compound 16, calcd.: 3.5. Found: 3.4. Compound 17, calcd.: 4.4. Found: 4.4. Compound 18, calcd.: 3.8. Found: 3.9. Compound 19, calcd.: 3.1. Found: 3.0. Compound 20, calcd.: 3.4. Found: 3.4. Chlorine analyses of salts: Compound 9, calcd.: 12.8. Found: 12.9. Compound 10, calcd.: 10.5. Found: 10.6. Compound 11, calcd.: 9.6. Found: 9.9. Compound 17, calcd.: 11.2. Found: 11.4. Compound 18, calcd.: 9.8. Found: 10.1. [c] Pyrrolidino. [d] Piperidino.



ucts to the substituted dihydroisoindole derivatives.

The preparation of most of the compounds shown in Table II (the benzydrols) and Table III (the triphenylcarbinols) proceeded smoothly. In Table IV are listed products having carbonyl functions but prepared through diverse reagents. Surprisingly the yield with the acid chloride was excellent in contrast to those from isocyanates. This may in part be due to the fact that only the reflux temperature of ether was employed in all cases. With the ester, ethyl *o*-bromobenzoate, the ketone and the tertiary alcohol were isolated.

Formation of the organomagnesium compounds was initiated by a brief heating of the *o*-*t*-aminomethylbromobenzenes with dry magnesium powder[12] at 60°, after which ether was added and the reaction completed under essentially the usual conditions. Traces of iodine were added during the heating period but that may not be necessary. After an hour or two of refluxing and stirring, a clear 0.1 to 0.2 *M* solution was obtained. The usual procedure was to add the Grignard solution to the ethereal solution of the reactant at room temperature.[13] After the addition was completed, the reaction mixture was stirred and heated for two additional hours. The mixture was then decomposed with saturated ammonium chloride solution.

The basic fractions were precipitated from ether by addition of ethereal hydrochloride acid solution. The free base mixture was then regenerated by alkali and the lower amines were distilled in *high vacuum*. The hydrochlorides of the basic products were obtained from the residues and crystallized from acetone–ether mixtures.

The products obtained from these Grignard reagents are somewhat diverse in character and might manifest a variety of potential physiological activities. Pharmacological screening data will be published at a later date.

Experimental[14]

Preparation of *o*-Bromobenzylamines. N-[*o*-Bromobenzyl]piperidine (Compound 5).—To a rapidly stirred solution of 72 g. (0.85 mole) of distilled piperidine in 500 ml. of anhydrous ether, was added slowly 100 g. (0.4 mole) of *o*-bromobenzylbromide in 500 ml. of anhydrous ether. The reaction mixture was stirred for an additional 2 hr. and left overnight. The piperidine hydrochloride precipitate was filtered off and washed thoroughly with ether (400 ml.). The combined ethereal solutions were washed with equal volumes of 5% sodium hydroxide solution, dried over potassium carbonate, and the solvent was removed on the steam bath, and finally *in vacuo*. The residual oil was distilled in tubular apparatus at 20-μ pressure, b.p. 72°.[15] The product weighed 99 g. (97% yield).

The hydrochloride of the base was prepared by adding ethanolic hydrogen chloride to a solution of 2 g. of the distilled base in 100 ml. of anhydrous ether. The product was twice crystallized from acetone–ether mixture in 95% yield, m.p. 245°.

Others in the series, shown in Table I, except compound 6, were prepared by the same procedure.

N-[*o*-Bromobenzyl]-N′-methylpiperazine (Compound 6).—The procedure was the same as above except that dry acetone was employed instead of ether as the solvent. The base was distilled at 12-μ pressure, b.p. 70–72°[15]; it melts at 35°.

Grignard Reagent (General Procedure). Magnesium Complex of *o*-Bromobenzylpiperidine.—To a 1-l. three-necked round-bottom flask equipped with a condenser having a calcium chloride tube, a bypass dropping funnel and a stopcock adapter to evacuate the flask, 1.3 g. (0.054 g.-atom) of magnesium powder was added. One-twentieth mole (12.7 g.) of *o*-bromobenzylpiperidine was placed in the bypass funnel. The flask was evacuated and heated by a low bunsen flame. The base was let in and the mixture stirred with a magnetic stirrer. (A crystal of iodine may be added, but it was not necessary in most cases.) After 15 min., 200 ml. of sodium-dried ether was added and the reaction mixture was refluxed vigorously. Within 1.75 hr. most of the magnesium had reacted giving a somewhat cloudy solution. The general procedure was to siphon out the solution under nitrogen pressure to a calibrated bypass funnel having a glass wool plug to filter the reagent, and thereafter admit it as required to stirred solutions of the compounds with which it was to be treated. The solution can be stored at 4° for several days without any significant loss of activity.

4-Chloro-2′-piperidinomethylbenzhydrol (Compound 18).—A solution of 7.0 g. (0.05 mole) of *p*-chlorobenzaldehyde in 150 ml. of anhydrous ether was placed in a 1-l. round-bottom flask equipped with a condenser, a bypass funnel having 0.05 mole of Grignard reagent (from 1.3 g. of magnesium and 12.7 g. of *o*-bromobenzylpiperidine), and a stopcock adapter to evacuate the flask of moisture. The flask was surrounded with a water bath at room temperature. The solution was stirred with a magnetic stirrer and the Grignard reagent was added dropwise over a duration of 1 hr. It was then warmed to 70° and stirred for an additional 1 hr. The reaction mixture was allowed to stand overnight at room temperature before it was decomposed with saturated ammonium chloride solution. The ether layer was separated and dried over anhydrous potassium carbonate. To the dry ethereal extract an ethereal solution of hydrogen chloride was added. The crude precipitate, weighing 16 g., was collected, redissolved in 250 ml. of water, filtered, and made basic. The base was taken into ether and dried over anhydrous potassium carbonate. After removal of the solvent, the mixture of bases was subjected to a high vacuum tubular distillation. About 1 g. of the forerun of benzylpiperidine, b.p. 72°, at 20-μ pressure was collected in the trap. The main product, weighing 11.8 g. (75% yield), came over at 5-μ pressure; furnace temperature, 140°.

(12) In our earlier experiments when magnesium turnings were employed the reaction time was four- to fivefold longer.

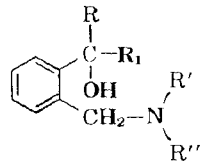
(13) The reaction of the complex with the carbonyl reactant is fairly rapid and the formation of an ether-insoluble complex ensues. This inverse addition aids the formation of a very finely divided suspension and mitigates any difficulty in stirring with a magnetic stirrer. The yields are decidedly better. Phenetole and *n*-pentyl ether were found unsuitable for the reaction.

(14) Melting points are uncorrected.

(15) Furnace temperature. N. B. Mehta and J. Zupicich, *Chemist-Analyst*, **50**, 84 (1961).

TABLE III

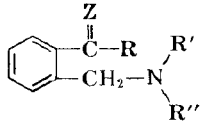
o-(SUBSTITUTED AMINOMETHYL)TRIPHENYLCARBINOLS



Compound	NR′R″	R	R_1	Yield, % (base)	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found
21	$(CH_3)_2N$	4-ClC_6H_4	C_6H_5	67	218–219[a]	$C_{22}H_{22}ClNO\cdot HCl$	**68.0**	68.0	**5.9**	**6.2**			9.2	9.4
22	$(CH_3)_2N$	4-ClC_6H_4	C_6H_5	81	158	$C_{22}H_{22}ClNO\cdot CH_3I$	**55.9**	56.0	**5.1**	**5.1**	2.8	2.8		
23	$(CH_2)_4N$[b]	C_2H_5	C_6H_5	48	220–221 (eff.)	$C_{26}H_{25}NO\cdot HCl\cdot 1/2H_2O$	**70.5**	70.7	**7.9**	**7.7**	4.1	4.3		
24	$(CH_2)_4N$[b]	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	49	168	$C_{26}H_{29}NO_3\cdot HCl$	71.1	**70.8**	**6.8**	**6.9**	3.2	3.5		
25	$(CH_2)_5N$[c]	4-ClC_6H_4	4-ClC_6H_4	54	232[d]	$C_{25}H_{25}Cl_2NO\cdot HCl$	**64.9**	64.5	**5.6**	**5.6**				
26	$(CH_2)_5N$[c]	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	72	177–178 (eff.)	$C_{27}H_{31}NO_3\cdot HCl\cdot 1/2H_2O$	70.2	**70.4**	7.2	7.4	3.0	2.9	**7.6**	7.7
27	$C_6H_{11}(CH_3)N$[e]	4-ClC_6H_4	C_6H_5	60	223–224	$C_{27}H_{30}ClNO\cdot HCl$	**71.1**	**70.8**	**6.8**	**6.7**				

[a] Also forms a stable hemihydrate. [b] Pyrrolidino. [c] Piperidino. [d] Forms a dihydrate m.p. 229–230° (eff.). Percentage moisture was determined by heating 150 mg. at 93° under 1-μ pressure for 3 hr. Calcd.: 7.2. Found: 7.3. [e] Methylcyclohexylamino. Analyses of bases. Compound 21, m.p. 181°, calcd.: C, 75.1; H, 6.3. Found: C, 75.0; H, 6.0. Compound 23, b.p. 125–128° under 25 μ, calcd.: C, 81.3; H, 8.5. Found: C, 80.8; H, 8.4. Compound 25, m.p. 182°, calcd.: C, 70.4; H, 5.9. Found: C, 70.4; H, 5.8. Compound 26, m.p. 174°, calcd.: C, 77.7; H, 7.4; N, 3.4. Found: C, 77.9; H, 7.4; N, 3.4. Compound 27, m.p. 119–120°, calcd.: C, 77.2; H, 7.2. Found: C, 76.9; H, 7.3.

TABLE IV



				Bases							Salts				
Compound	NR′R″	R	Z	Yield, %	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
28	$(CH_2)_4N$[a]	NHC_6H_5	O	66	100–101	$C_{18}H_{20}N_2O$	77.1	**76.9**	7.2	**6.9**	157[b] (eff.)	$C_{18}H_{20}N_2O\cdot HCl\cdot 1/2H_2O$	66.4	66.6	**6.8**	6.5
29	$(CH_2)_4N$[a]	$NHCH_2C_6H_5$	S	40	126	$C_{19}H_{22}N_2S$	73.6	**73.8**	7.1	**6.9**	182–183	$C_{19}H_{22}N_2S\cdot HCl$	65.9	65.9	**6.6**	6.5
30	$(CH_2)_5N$[c]	2-BrC_6H_4[d]	O	40	120–5/0.1[e] μ	$C_{19}H_{20}BrNO$	63.6	63.2	5.6	5.9	218–219	$C_{19}H_{20}BrNO\cdot HCl$	57.8	58.1	**5.3**	5.2
31	$(CH_2)_5N$[c]	2-ClC_6H_4[f]	O	90							221–222	$C_{19}H_{20}ClNO\cdot HCl$	65.2	65.3	**6.0**	6.0
32	$(CH_2)_5N$[c]	2-ClC_6H_4[f]	O								174–175	$C_{19}H_{20}ClNO\cdot CH_3I$	52.8	52.7	**5.0**	4.8
33	$(CH_2)_5N$[c]	NHC_6H_5	O	56[g]	119–120	$C_{19}H_{22}N_2O$	77.6	77.7	7.5	7.5	181–182 (eff.)	$C_{19}H_{22}N_2O\cdot HCl\cdot 1/2H_2O$	67.3	67.5	7.1	6.8
34	$(CH_2)_5N$[c]	$NHCH_2C_6H_5$	S	60[h]	149–150	$C_{20}H_{24}N_2S$	74.1	**74.0**	7.4	7.4	196[i]	$C_{20}H_{24}N_2S\cdot HCl$	**66.6**	66.5	**6.9**	6.8
35	$(CH_2)_5N$[c]	α-$C_{10}H_7NH$	S	40							249[j]	$C_{23}H_{24}N_2S\cdot HCl$	**69.6**	69.3	**6.3**	6.2

[a] Pyrrolidino. [b] Nitrogen calcd.: 8.6. Found: 8.8. [c] Piperidino. [d] Ethyl *o*-bromobenzoate (reagent). [e] Boiling point, furnace temperature. [f] *o*-Chlorobenzoyl chloride (reagent). [g] Nitrogen analysis (base) calcd.: 9.5. Found: 9.4. [h] Nitrogen calcd.: 8.6. Found: 8.3. [i] Nitrogen calcd.: 7.7. Found: 7.6. [j] Nitrogen calcd.: 7.1. Found: 7.0.

The hydrochloride of the base was prepared by the addition of ethereal hydrogen chloride solution to 1 g. of the distilled base in 150 ml. of anhydrous ether. It was recrystallized from ethanol–ether as a hemihydrate, needles, m.p. 120–122° (eff.).

4-Chloro-2′-piperidinomethylbenzhydrol Methiodide (Compound 19).—To a solution of 2 g. of the distilled base (compound 18) in 150 ml. of dry acetone, excess methyl iodide was added and refluxed for 2 hr. The reaction mixture was left overnight at room temperature. After removal of the solvent *in vacuo*, the residue was crystallized from methanol–ether; 2.2 g. of thick cubic crystals were collected, m.p. 182°.

4-Chloro-2′-dimethylaminomethyltriphenylcarbinol Hydrochloride (Compound 21).—The procedures for the preparation of the Grignard reagent from 5.85 g. (0.025 mole) of *o*-bromobenzyldimethylamine and its reaction with 5.3 g. (0.025 mole) of 4-chlorobenzophenone were similar to those described above. The product mixture was extracted with ether and converted to hydrochloride salts. The mixture was dissolved in water, filtered, made basic, extracted with ether, and dried over anhydrous potassium carbonate. After evaporating the solvent, dimethylbenzylamine was removed in high vacuum. The carbinol residue was recrystallized from ether, 5.7 g. (67% yield), m.p. 180–181°. With concentrated sulfuric acid, it gave a bright red color.

The hydrochloride of the base was prepared by the addition of ethereal hydrogen chloride solution to an ethereal solution of the base. It was recrystallized from methanol–acetone to give crystals, m.p. 218–219°.

N-Benzyl-*o*-piperidinomethylthiobenzamide (Compound 34).—The Grignard reagent prepared from 12.7 g. (0.05 mole) of *o*-bromobenzylpiperidine and 1.3 g. (0.05 g.-atom) of magnesium powder in 500 ml. of dry ether was added to a solution of 7.45 g. (0.05 mole) of benzyl isothiocyanate in 150 ml. of dry ether. The reaction mixture was stirred vigorously during the gradual addition which required 0.5 hr. A colorless precipitate appeared immediately on addition. After stirring overnight at room temperature, the reaction mixture was decomposed by the addition of 10 g. of ammonium chloride in 30 ml. of water. The reaction mixture was extracted with an additional 500-ml. portion of ether, and dried over potassium carbonate. On concentration and cooling, yellow needles separated. Recrystallization from acetone–ether gave 9 g. (60% yield), m.p. 149–150°. The entire product was converted to the hydrochloride and recrystallized from methanol–ether, m.p. 196°.

***o*-Piperidinomethylbenzanilide (Compound 33).**—To a solution of 5.65 g. (0.0475 mole) of phenyl isocyanate in 200 ml. of dry ether, 0.0475 mole of Grignard reagent prepared from o-bromobenzylpiperidine in 212 ml. of ether was added dropwise with rapid stirring at room temperature. A white turbidity developed on addition. After refluxing for 1.5 hr., the reaction mixture was cooled and decomposed with saturated ammonium chloride solution. The reaction mixture was extracted with an additional 500 ml. of ether, and dried over potassium carbonate. On addition of pentane to the cool concentrated filtrate, 7 g. of white needles separated, m.p. 116–117° (yield 56%). Recrystallization from ether–pentane mixtures gave the product melting at 119–120°.

***o*-Piperidinomethylbenzylanilide Methiodide.**—An ethereal solution of 2.8 g. (0.0095 mole) of *o*-piperidinomethylbenzanilide base (compound 33) was reduced with lithium aluminum hydride. The reduced base was treated with methyl iodide in dry acetone at room temperature. Recrystallization from methanol gave crystals, m.p. 193–194° dec.

Anal. Calcd. for $C_{20}H_{27}N_2I$: C, 56.9; H, 6.4. Found: C, 57.3; H, 6.8.

2-Bromophenyl-2′-piperidinomethylbenzophenone (Compound 30).—To a solution of 10.8 g. (0.047 mole) of ethyl *o*-bromobenzoate in 200 ml. of anhydrous ether was added the Grignard reagent from 1.27 g. of magnesium and 12.7 g. (0.05 mole) of *o*-bromobenzylpiperidine. The reaction mixture was worked up as before. Fractional distillation of the oily basic residue from ether gave a forerun of the reactant and benzylpiperidine followed by 6.7 g. (35% yield) of the ketone, b.p. 120–125°[15] at 0.11-μ pressure.

The residue, 3 g., on crystallization from ether–pentane mixture gave needles, m.p. 85–86°, characterized as bis-(2-piperidinomethylphenyl)-2′-bromophenylcarbinol.

Anal. Calcd. for $C_{31}H_{37}BrN_2O$: C, 69.8; H, 6.98. Found: C, 70.1; H, 7.03.

The dihydrochloride of this carbinol crystallized as a hydrate and melted at 122° (eff.).

Anal. Calcd. for $C_{31}H_{37}BrN_2O \cdot 2\ HCl \cdot 2.5\ H_2O$: C, 57.1; H, 6.76. Found: C, 57.4; H, 6.55.

2-Chloro-2′-piperidinomethylbenzophenone Methiodide (Compound 32).—Excess methyl iodide in dry acetone was added to 0.5 g. of 2-chloro-2′-piperidinomethylbenzophenone base (compound 31) and left overnight at room temperature. Crystallization from hot acetone gave thick prisms, m.p. 174–175°.

2-Chloro-2′-piperidinomethylbenzhydrol Methiodide.—One gram of the base, 2-chloro-2′-piperidinomethylbenzophenone (compound 31), was reduced with sodium borohydride in absolute ethanol. The benzhydrol product was quaternized with methyl iodide in dry acetone. Recrystallization from methanol–acetone mixtures gave crystals, m.p. 199–200°.

Anal. Calcd. for $C_{19}H_{22}ClNO \cdot CH_3I$: C, 52.5; H, 5.46. Found: C, 52.5; H, 5.56.

Methyl-*o*-piperidinomethylbenzoate Methiodide.—To an Erlenmeyer flask containing excess powdered Dry Ice, 0.05 mole of the Grignard reagent prepared from *o*-bromobenzylpiperidine was added and shaken vigorously. After 48 hr. the solution was acidified with 10% hydrochloric acid and concentrated to dryness *in vacuo*. The entire mass was then converted to its potassium salt. The dry solid residue was suspended in acetone and treated with excess methyl iodide. The acetone soluble fraction was crystallized from acetone–ether mixtures to give an 85% yield of the product, m.p. 141–142°.

Anal. Calcd. for $C_{15}H_{22}INO_2$: C, 48.0; H, 5.9; N, 3.7. Found: C, 48.0; H, 5.9; N, 3.3.

1-[*p*-Chlorophenyl]dihydroisoindole Spiropentamethylene Ammonium Tosylate Hemihydrate.[16]—A mixture of 2.5 g. of the base (compound 18) and 3 g. of *p*-toluenesulfonyl chloride in 100 ml. of triethylamine was warmed on a steam bath for 15 min. when a voluminous precipitate appeared. After 1 hr., the solution became clear and the crystalline precipitate separated. The solvent was removed *in vacuo* and the residue was repeatedly triturated with ether. The crystalline product mixture was next triturated with acetone and the insoluble triethylamine hydrochloride was separated. The filtrate on evaporation gave 4 g. of crystalline residue. After removal of traces of triethylamine hydrochloride by vacuum sublimation it was recrystallized from acetone–ether mixtures, m.p. 67–68° (eff.) in 90% yield as a hemihydrate.

Anal. Calcd. for $C_{26}H_{28}SNO_3 \cdot 0.5H_2O$: C, 65.2; H, 6.1. Found: C, 65.1; H, 5.9.

4-Chloro-2′-[methylcyclohexylaminomethyl]triphenyl-α-acetoxymethane Hydrochloride.—A solution of 2 g. of the hydrochloride salt (compound 27) and 5 ml. of acetyl chloride in 50 ml. of nitromethane in a pressure bottle was kept at 40° for 16 hr. After the removal of the solvent *in vacuo* the white crystalline product was repeatedly triturated with

(16) (a) N. B. Mehta and R. E. Brooks, *J. Org. Chem.*, **27**, 1266 (1962); (b) N. B. Mehta, R. E. Brooks, J. Z. Strelitz, and J. W. Horodniak, presented before the Division of Organic Chemistry at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 1962, paper 43.

ether. Crystallization from acetone-ether mixtures gave 2.1 g. of colorless, fluffy needles in 90% yield, m.p. 230°.

Anal. Calcd. for $C_{29}H_{31}NO_2 \cdot HCl$: C, 69.9; H, 6.6; N, 2.8. Found: C, 69.9; H, 7.0; N, 3.0.

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Condensations of Aromatic Aldehydes with Oxazolines and a New Synthesis of Cinnamic Acids

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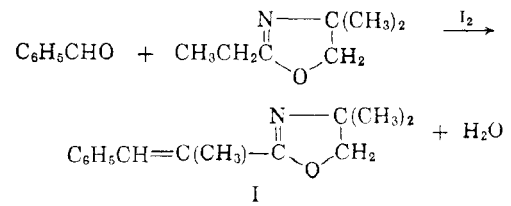
Benzaldehyde and other aromatic aldehydes have been condensed with a variety of 2-alkyl-2-oxazolines using suitable catalysts. Condensation occurs at the *alpha* position of the 2-alkyl substituent yielding phenylethenyloxazolines. Hydrolysis of these phenylethenyloxazolines gives the cinnamic acids in high yield.

According to a patent by Hamer and Rathbone[1] 2-methyl-2-oxazoline methiodide can be condensed with *p*-dimethylaminobenzaldehyde to yield the quaternary salt of 2-(2-*p*-dimethylaminophenylethenyl)-2-oxazoline.

Wiley and Bennett,[2] in referring to this work of Hamer and Rathbone, state that "condensations of this type have not been studied by other investigators or with compounds other than the alkiodides of 2-methyl-2-oxazoline". Cornforth[3] indicates that the work of Hamer and Rathbone "is a reaction which has no analogy among acyclic imino ethers."

2-(1,1-Dichloro-2-*p*-nitrophenyl-2-hydroxyethyl)-2-oxazoline has been prepared by the reaction of *p*-nitrobenzaldehyde with 2-dichloromethyl-2-oxazoline.[4] The reaction of an aromatic aldehyde with a nonquaternized alkyloxazoline to yield a phenylethenyloxazoline seemingly has not previously been reported.

Benzaldehyde was condensed with 2-ethyl-4,4-dimethyl-2-oxazoline. After twenty-three hours of reflux at temperatures of 133–153°, only a 16% yield of the desired 2-(1-methyl-2-phenylethenyl)-2-oxazoline (I) was isolated. Only a 32% yield of crude I was obtained when the reaction was carried out in the presence of acetic anhydride. A satisfactory reaction with a yield as high as 76% was achieved by the use of catalytic amounts of iodine (equation 1). Analytical results agree with the theoretical values. α-Methylcinnamic acid is obtained on acid-catalyzed hydrolysis (equation 2). Other catalysts for this reaction include *p*-xylenesulfonic acid, zinc chloride, and sodium bisulfate. These may be better than iodine but have not been studied as extensively. Sodium acetate was not an effective catalyst.



(1)

I

This condensation was successfully extended to other aldehydes and oxazolines. Hydrolysis of the phenylethenyloxazolines yielded the cinnamic acids without difficulty. The cinnamic acids obtained have melting points which agree with the literature values for products established as having, or provisionally assigned, the *trans* (phenyl/COOH) structure. Presumably the phenylethenyloxazolines have a *trans* (phenyl/oxazolyl) structure.

If the cinnamic acid is the desired product, it is convenient to hydrolyze the product mixture without isolation of the intermediate oxazoline derivative. This procedure is illustrated with *m*-nitrobenzaldehyde. At a 1:1 mole ratio of aldehyde to oxazoline, a 61% yield of α-methyl-*m*-nitrocinnamic acid was obtained. A 90% yield was obtained using a 1:2 mole ratio.

All of the other reactions were carried out at a 1:1 mole ratio. Further study of mole ratios, reaction conditions and catalysts would probably result in improved yields. The use of sodium bisulfate in place of iodine, for example, merits further attention.

This synthesis of cinnamic acids may be compared with that of Perkin[5] and Doebner.[6]

Experimental[7]

Starting Materials.—2-Ethyl-4,4-dimethyl-2-oxazoline and 2-ethyl-4-methyl-4-hydroxymethyl-2-oxazoline were

(1) F. M. Hamer and R. J. Rathbone, British Patent 541,330 (1941).

(2) R. H. Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 461 (1949).

(3) J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y., 1957, p. 389.

(4) H. Bretschneider, G. Piekarski, and K. Biemann, *Monatsh.*, **85**, 882 (1954); *Chem. Abstr.*, **49**, 15860 (1955).

(5) *Cf.* J. R. Johnson, "Organic Reactions," Vol. 1, Roger Adams, ed., J. Wiley & Sons, Inc., New York, N. Y., 1942, pp. 210–265.

(6) *Cf.* W. J. Gensler and E. Berman, *J. Am. Chem. Soc.*, **80**, 4949 (1958).

(7) All melting points were taken on a Fisher–Johns melting point apparatus.