Ammonium Salt of 2-Methyl-3-hydroxy-4-formyl-5-pyridylmethylphosphoric Acid Using Manganese Dioxide:—Pyridoxamine dihydrochloride (2.5 g.) was dissolved in 25 g. of anhydrous phosphoric acid as described above. After standing for several days at room temperature under anhydrous conditions, the mixture was poured into about 200 ml. of a mixture of ice and water. A solution of 30% sodium hydroxide was added carefully until the reaction mixture was about *p*H 6.

One gram of manganese dioxide was added and the mixture was heated at 60° for 20 minutes with frequent shaking. The manganese dioxide was replaced by a light-colored inorganic solid, and the colorless solution became yellow-brown due to the presence of the aldehyde phosphate. The solution was cooled, filtered from the inorganic salt, diluted with an equal volume of water, and re-acidified to congo red with phosphoric acid. The organic material was adsorbed on Darco G-60 as described above, and isolated in an identical manner. The yield of freeze-dried residue was 2.6 g. (88%) $\lambda_{\max.}^{H_2O}$ (*p*H 11) 2300 Å., *E*% 300; shoulder 2650–2750 Å., *E*% 90–70; plateau 2850–3100 Å., *E*% 38; $\lambda_{\max.}$ 3900 Å., *E*% 180.

Isolation of Codecarboxylase as the Calcium Salt.—Twenty-five grams of pyridoxamine dihydrochloride was dissolved in 250 g. of anhydrous phosphoric acid as described above, and was converted to the aldehyde phosphate by means of manganese dioxide oxidation. Instead of concentrating the ammonia eluate to dryness, however, it was concentrated under reduced pressure to a volume of about 1 liter. The concentrate was acidified to about *p*H 4 with dilute acetic acid, and to it was added a solution of 18.5 g. of calcium acetate in water. Additional acetic acid may be added if necessary to maintain solution. A small amount of amorphous insoluble material was removed by filtration through Super-cel, and the clear filtrate was diluted with three volumes of ethyl alcohol. The mixture was allowed to stand overnight in the refrigerator. The precipitate was centrifuged, washed with a mixture of alcohol and water, with a mixture of alcohol and ether, finally with ether, and dried in a vacuum oven at 40–45°. The yield of bright yellow calcium salt of codecarboxylase was 29 g. (97%); $\lambda_{\max.}^{H_2O}$ (*p*H 11) 2280 Å., *E*% 375; shoulder 2650–2750 Å., *E*% 90–60; $\lambda_{\max.}$ 3075 Å., *E*% 37; $\lambda_{\max.}$ 3900 Å., *E*% 164.

Codecarboxylase Oxime.—Five grams of pyridoxamine dihydrochloride was phosphorylated in 50 g. of the anhydrous phosphoric acid as described above, and was oxidized to the aldehyde with 2 g. of manganese dioxide. This oxidized solution was filtered from the inorganic salts and made just acid to congo red paper with hydrochloric acid. The volume of the resulting solution was about 400 ml. To this solution was added 4 g. of hydroxylamine hydrochloride dissolved in a little water. On scratching, crystallization of the oxime took place. After standing at room temperature for several hours, the crystals were collected, washed and dried. The yield of codecarboxylase oxime was 2.6 g. (50%); m.p. 218° dec. A melting point of a mixture of this sample with a known sample of codecarboxylase oxime showed no depression.

RAHWAY, N. J.

RECEIVED MAY 23, 1951

[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORIES, LOUISIANA STATE UNIVERSITY]

The Synthesis of Some Simple and Mixed Ethers as Contact Insecticides[1]

BY TIEN-CHIH CHEN[2a] AND W. T. SUMERFORD[2b]

The phenomenal activity of DDT (2,2-bis-(*p*-chlorophenyl)-1,1,1-trichloroethane) as a contact insecticide has been attributed to its neurotoxic bis-(*p*-chlorophenyl)-methylene group and its lipophilic trichlorinated methyl radical.[3]

Attempts to combine these insecticidally-active groups in other molecules to obtain additional, and possibly improved, insecticides has met with varying degrees of success, and in some instances with complete failure. In projecting this general effort to obtain substitutes for DDT and to prepare compounds which might be toxic to DDT-resistant insects, especially house flies,[4] it seemed worthwhile to synthesize a series of benzyl aryl ethers and allyl aryl ethers having one or more halogen atoms in either or both of the aliphatic and aromatic hydrocarbon radicals. The benzyl aryl series of compounds would possess a neurotoxic haloaryl group, an ether linkage having lipophilic properties in the Overton–Meyer concept of narcosis, as well as a benzyl radical, of which the alcohol and other derivatives are known to be neurotropic in character. In addition to the haloaryl group and the ether linkage, the allyl aryl series would depend for activity upon a 2- or a 3-chloroallyl grouping, both of which might be expected to have a fumigant action against insects.[5] Added support for the possible insecticidal activity of these series of compounds is found in the potent contact insecticides: rotenone, 2-butoxy-2′-thiocyanodiethyl ether[6] and 2,2-bis-(*p*-methoxyphenyl)-1,1,1-trichloroethane,[7] all of which have one or more ether linkages in their structures.

A series of benzyl and halobenzyl ethers with phenol, halophenols and nitrophenols has been credited in the patent literature with having general insecticidal activity[8]; and *p*-chlorobenzyl *p*-chlorophenyl ether has been shown to be active against the citrus red mite.[9] The 2-chloroallyl ethers of phenol, certain alkyl-, aryl-, chloro- and nitro-substituted phenols have been patented as fly sprays[10] as have the related compounds: 2-chloroallyl 2-(*p*-chlorophenyl)-ethyl ether, 2-chloroallyl 2-(2-chloro-4-*t*-butylphenyl)-ethyl ether and 2-(3-chloro-2-methylallyloxy)-2′-(2-phenoxy)-diethyl ether.[11]

The nine benzyl aryl ethers and the seven chloroallyl aryl ethers prepared in this study, which are

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[1] This paper has been constructed from the Doctorate dissertation presented by Tien-Chih Chen to the Louisiana State University in August, 1949.

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[3] P. Läuger, H. Martin and P. Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

[4] Frank H. Babers, "Development of Insect Resistance to Insecticides," Publication E-776, Bur. Entomol. and Plant Quarantine, U. S. Dept. of Agri., Washington, D. C., 1949, 31 pp.

[5] O. I. Snapp, "Publication E-558, Bur. Entomol., and Plant Quarantine," U. S. Dept. of Agri., Washington, D. C., 1942, 4 pp.

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[7] E. A. Prill, A. Hartzell and J. M. Arthur, *Science*, **101**, 464 (1945).

[8] W. F. Hester, U. S. Patent 2,243,479 (1941).

[9] R. L. Metcalf, *J. Econ. Entomol.*, **41**, 872 (1948).

[10] G. H. Coleman, *et al.*, U. S. Patent 2,207,721 (1940).

[11] C. L. Moyle and G. H. Coleman, U. S. Patent 2,244,309 (1941).

TABLE I

THE PHYSICAL CONSTANTS, ANALYSES AND INSECTICIDAL ACTIVITY OF SOME BENZYL ARYL ETHERS

Ether	Method of prepn.	Yield, %	M.p., °C.	$n^{25}\text{D}$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Mortality, % Larvae[a]	Beetles[b]	Flies[c]
α,α-Dichlorobenzyl *p*-chlorophenyl	II	62	......	1.5269	54.29	54.88	3.16	3.62	5	15	0
o-Chlorobenzyl *p*-chlorophenyl	I	50	......	1.5897	61.68	61.52	3.98	4.19	30	10	100
o-Chlorobenzyl *p*-bromophenyl	I	50	......	1.6072	53.47	52.40	3.39	3.42	25	23	100
Benzyl 2,4-dichlorophenyl	I	62	60–61[d]	....	61.68	61.41	3.98	4.08	5	0	0
α,α-Dichlorobenzyl 2,4-dichlorophenyl	II	78	......	1.5360	48.48	48.15	2.50	2.69	5	12	12
o-Chlorobenzyl 2,4-dichlorophenyl	I	71	63–65[e]	....	54.29	54.00	3.15	3.24	10	6	15
Benzyl 2,4,5-trichlorophenyl	I	66	74–76[e]	....	54.29	54.48	3.15	3.16	15	5	30
o-Chlorobenzyl 2,4,5-trichlorophenyl	I	70	123–125[e]	....	...	...	Cl, 44.04	44.40[f]	45	25	80
Benzyl 1,2,3,4,5-pentachlorophenyl	I	60	164–166[g]	....	...	...	Cl, 49.73	49.14[f]	20	0	100
DDT	..	..	......	....	...	...	..	....	55	60	100

[a] These percentage mortalities were obtained by holding separately a sample of 10 third instar *Anopheles quadrimaculatus* larvae for 48 hours in 200 ml. of water containing 0.1 p.p.m. of the compound. [b] These percentage mortalities were obtained by confining separately a sample of 20 adult confused flour beetles for 24 hours on filter paper impregnated with the individual compound at a dose of 30 mg./sq. in. [c] These percentage mortalities were obtained by exposing separately a sample of 30 normal adult house flies for 30 minutes on a glass panel having a 7-day-old, 50 mg./225 sq. in. deposit of the compound. The flies were held for 12 hours under optimum conditions for recovery prior to making mortality counts. [d] Recrystallized from isobutyl alcohol. [e] Recrystallized from ethanol. [f] The excessive chlorine content of these ethers necessitated analyses for this elemental constituent. [g] Recrystallized from a mixture of benzene and ethanol.

TABLE II

THE PHYSICAL CONSTANTS, ANALYSES AND INSECTICIDAL ACTIVITY OF SEVERAL CHLOROALLYL ARYL ETHERS

Ether	Method of prepn.	Yield, %	M.p., °C.	$n^{25}\text{D}$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Mortality,[a] % Larvae	Beetles	Flies
2-Chloroallyl *p*-chlorophenyl	I	53	......	1.5426	53.53	52.98	3.97	3.96	10	4	5
3-Chloroallyl *p*-chlorophenyl	III	60	......	1.5541	53.53	52.84	3.97	4.15	40	100	29
3-Chloroallyl *p*-bromophenyl	I	42	......	1.5686	44.94	44.49	3.35	3.14	45	100	0
2-Chloroallyl 2,4-dichlorophenyl	I	60	......	1.5567	45.51	45.60	2.97	3.01	5	37	12
3-Chloroallyl 2,4-dichlorophenyl	III	70	......	1.5628	45.51	45.75	2.97	3.19	55	60	100
3-Chloroallyl 1,2,3,4,5-pentachlorophenyl	III	66	133–135[b]	....	Cl, 62.41	62.42	...	..	15	25	0
3-Chloroallyl *p*-benzylphenyl	III	50	......	1.5437	Cl, 74.27	74.53	5.84	5.92	50	37	100
DDT	...	..	......	....	...	...	...	..	55	60	100

[a] These determinations were made by the procedures described in the corresponding footnotes in Table I. [b] Recrystallized from petroleum ether.

listed in Tables I and II, respectively, were synthesized by one or more modifications of the Williamson method. These several modifications are described in the experimental part. The yields of the ethers were satisfactory, and, in general, their isolation and purification were not difficult. The dropwise addition of the alkyl halide to the metallic phenolate, as described in Modification II, proved to be advantageous in the preparation of several of the ethers, both from the standpoint of yield and purity of the product. The method of preparation, the percentage yield, a physical constant, analytical results, and some biological data of the benzyl ethers are listed in Table I and those of the chloroallyl ethers are listed in Table II.

Modification I.—Six and six-tenths grams (0.1 mole) of potassium hydroxide was added to 50 ml. of 95% ethanol contained in a 250-ml. round-bottomed flask fitted with a reflux condenser by means of a ground-glass joint. The mixture was heated to dissolve the alkali and allowed to cool. One-tenth mole of the appropriately substituted phenol, dissolved in 50 ml. of 95% ethanol, was added to the alcoholic alkali. To this solution was added 0.1 mole of the benzyl halide or the dichloropropene. The resulting mixture was refluxed until the potassium halide ceased to separate, the required period being from one to five hours. The potassium halide was removed by filtration and the alcoholic filtrate was poured onto chipped ice. The ethers which separated as solids were collected by filtration, dried on absorbent paper and then purified by recrystallization from a lower aliphatic alcohol or other appropriate solvent. The liquid ethers were extracted with ethyl ether, dried over anhydrous sodium sulfate, and then purified, after removal of the solvent, by fractional distillation in a Hickman vacuum still.

Modification II.—In a 250-ml., round-bottomed, two-necked flask, fitted with a water-cooled condenser and a dropping funnel, was placed an alcoholic solution of 0.1 mole of potassium halophenolate prepared by dissolving equivalent quantities of the halophenol and potassium hydroxide in 80 ml. of 95% ethanol. This solution was heated to boiling and to it was added dropwise over a period of two hours 0.1 mole of the benzyl or substituted allyl halide previously dissolved in 20 ml. of 95% ethanol. The mixture was refluxed for an additional period of one hour or until there was no evidence of potassium halide formation. The potassium halide was removed and the ether collected and purified in the manner described above.

Modification III.—One-tenth mole of the phenol and an equivalent quantity of the benzyl or substituted allyl halide was dissolved in 100 ml. of purified acetone. To this solution was added 0.1 mole of freshly fused, powdered potassium carbonate, and the resulting mixture was refluxed on a water-bath for eight hours. The mixture was filtered free of insoluble material, and the desired ether collected and purified as described under Modification I.

Insecticidal Activity.—When tested under comparable conditions, none of the ethers described in this paper was superior to DDT as a mosquito larvicide. Two of the compounds, 3-chloroallyl *p*-chlorophenyl ether and the corresponding *p*-bromo-derivative, were approximately twice as active as DDT against the confused flour beetle. The 3-chloroallyl ethers with 2,4-dichlorophenol and *p*-benzylphenol; the *o*-chlorobenzyl ethers with *p*-chlorophenol and *p*-bromophenol and the benzyl ether with 1,2,3,4,5-pentachlorophenol were roughly equal to DDT in contact toxicity toward normal house flies.

The 3-chloroallyl ethers were more toxic toward insects than the isomeric 2-chloro compound, possibly due to a difference in their dehydrochlorination rates. The substitution of multiple chlorine atoms in the phenyl radical failed to enhance the activity of the resulting compounds except in the case of benzyl 1,2,3,4,5-pentachlorophenyl ether which was quite toxic toward houseflies. The substitution of a benzyl group for the 3-chloroallyl group in the corresponding *p*-halophenyl ethers failed to reduce their high activity. In some instances, the introduction of an *o*-chloro atom in the benzyl group yielded a more toxic molecule, notably against houseflies.

Two of the compounds, 3-chloroallyl 2,4-dichlorophenyl ether and *o*-chlorobenzyl 2,4-dichlorophenyl ether, when tested at the rate of 20 mg. of the ether and 200 mg. of DDT per sq. ft., gave considerably higher mortalities than did DDT alone against DDT-resistant flies.

Acknowledgments.—The authors are indebted to Dr. S. W. Simmons, Director, and to Dr. R. W. Fay of the Technical Development Services of the Communicable Disease Center, U. S. Public Health Service, for making available the laboratory facilities and procedures used to determine the insecticidal activity of the compounds reported here.

BATON ROUGE, LOUISIANA RECEIVED APRIL 4, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF IDAHO]

Condensation of Aldehydes with Ketones. Methylanilinomagnesium Bromide as a Condensing Agent

BY ARNOLD T. NIELSEN, CATHERINE GIBBONS[1] AND CORT A. ZIMMERMAN[1]

Ten new ketols have been prepared using the condensing agent methylanilinomagnesium bromide for the condensation of aldehydes with certain "unreactive" ketones which usually do not react using ordinary catalysts. With the present procedure the reaction was found to be limited to those ketones which do not readily self-condense in the presence of the condensing agent. Seven new diketones prepared from the ketols have been saponified and their course of cleavage studied.

In the presence of a basic catalyst such as sodium hydroxide many aldehydes have been condensed with methyl, cyclic and certain ethyl ketones to give good yields of condensation product.[2] On the other hand, some ketones are less reactive and give no reaction or very low yields of condensation product under the same conditions.[3] In such ketones the carbonyl group is generally attached to groups larger than ethyl. The present paper describes a method by which several aldehydes have been condensed with some of these "unreactive" ketones using methylanilinomagnesium bromide as the condensing agent.

Methylanilinomagnesium bromide has previously been employed in ketone–ketone condensations,[4,5,6,7] but apparently not in aldehyde–aldehyde or aldehyde–ketone condensations. In the ten examples listed in Table I nine different aldehydes and six different ketones were used. The ketols were isolated in yields of 15–88% (62–88% in seven cases). The general reaction procedure was first to add a small excess of the ketone to a freshly prepared ether–benzene solution of one mole of methylanilinomagnesium bromide and then add approximately two-thirds mole of pure aldehyde to the cold (−10°) solution.

In certain cases the condensation failed to give the desired ketol. In the attempted condensation of *n*-butyraldehyde with acetone, 3-pentanone[8] and acetophenone[8] and of propionaldehyde with 3-heptanone the ketone condensed with itself before reacting with the aldehyde. The ketols formed by the self-condensation of 3-pentanone and 3-heptanone were isolated and identified. Acetophenone was recovered, but not its ketol which decomposes on distillation.[9] Reaction of benzaldehyde with propiophenone probably gave a ketol, but attempts to distil it resulted in its decomposition into aldehyde and ketone. Attempted condensations of benzophenone with propionaldehyde and of fluorenone with isovaleraldehyde gave no aldol. The procedure was similar to Colonge's[5] by which he prepared mixed ketols when condensing benzophenone and fluorenone with various other ketones. Unreacted ketone was recovered in our experiments and the aldehyde was consumed by a side reaction to form an amine.

In most cases the unreacted aldehyde was not recovered, but removed by a side reaction involving the formation of a tertiary amine. The structure of the amine by-product was proved in two cases and it is likely that the same type of compound was formed in other instances. This side reaction occurred to the greatest extent in those cases where the least amount of aldehyde–ketone condensation

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(1) Research Corporation Fellow, 1949–1950.

(2) For a literature survey see A. T. Nielsen, Thesis, University of Washington, Seattle, 1947.

(3) *Cf.* S. G. Powell and A. T. Nielsen, THIS JOURNAL, **70**, 3627 (1948).

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(8) Ethylanilinomagnesium bromide was used as the condensing agent.

(9) J. Colonge, *Compt. rend.*, **190**, 1414 (1933).