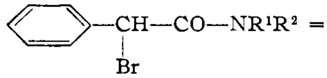
dry toluene. When all of the potassium had reacted, 1 mole of freshly distilled α-bromophenylacetyl chloride dissolved in an equal volume of dry toluene was added dropwise with constant stirring. When the initial reaction had subsided, the mixture was refluxed with continuous stirring for four to ten hours. Apparently little reaction occurred after the four hours heating period but no decrease in yield was noted when the longer reflux time was used.

The reaction mixture was filtered to remove the precipitated sodium salts and the toluene was subsequently distilled under a water-pump vacuum. The residual liquid was distilled *in vacuo* and further purified by two fractional distillations. The hydrochlorides of these esters were too hydroscopic to handle conveniently.

α-Bromophenylacetamide.—A concentrated solution of 2 moles of ammonium hydroxide was cooled to −10°. This solution was stirred vigorously while 1 mole of α-bromophenylacetyl chloride was added dropwise. Care was taken to keep the temperature of the reaction mass below 0°. After stirring for two hours at this temperature the reaction was allowed to warm to room temperature. The crystals which had formed were collected and recrystallized from alcohol to give glistening white crystals of α-bromophenylacetamide.

N,N-Diethyl α-Bromophenylacetamide.—A solution of 1 mole of α-bromophenylacetyl chloride in an equal volume of carbon tetrachloride was cooled to −10° and a solution of 2 moles of diethylamine in carbon tetrachloride added dropwise with constant stirring so as to keep the temperature below 0°. After stirring for two hours at this temperature, water was added to dissolve the diethylamine hydrochloride. The organic layer was separated, dried and the carbon tetrachloride distilled *in vacuo*. The liquid residue was fractionated at reduced pressure to give N,N-diethyl-α-bromophenylacetamide.

TABLE II



$C_6H_5-CH(Br)-CO-NR^1R^2 = C_8H_6BrNOR^1R^2$

R^1	R^2	Yield, %	M. p.,[a] °C.	% Bromine Calcd.	% Bromine Found	% Nitrogen Calcd.	% Nitrogen Found
H	H	92	148[b]	37.34	37.49	6.55	6.54
C_2H_5	C_2H_5	49	155–160[c]	29.59	29.68	5.18	5.22
H	C_6H_5	40	123	27.53	27.65	4.83	4.90
C_6H_5	C_6H_5	32	140	21.82	21.95	3.82	3.87
H	CH_3	68	74	35.07	35.17	6.15	6.23

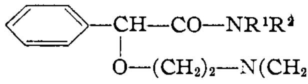
[a] Corrected. [b] First prepared by Darapsky, *J. prakt. Chem.*, **96**, 285 (1917). [c] B. p. at 6 mm.

The remaining amides were prepared in an analogous manner. Data for all of the amides are given in Table II.

α-(2-Piperidinoethoxy)-phenylacetamide.—One mole of α-bromophenylacetamide was refluxed with 1 mole potassium 2-piperidinoethoxide suspended in xylene for two hours. The product was extracted from the xylene with 5% hydrochloric acid. Neutralization of this acid extract gave a white precipitate. Recrystallization from alcohol gave white flakes of the expected α-(2-piperidinoethoxy)-phenylacetamide.

Other amides were prepared in the same manner and data concerning these are given in Table III. N,N-Diphenyl-α-bromophenylacetamide failed to give the expected product. The yields in all other cases were approximately 50%.

TABLE III



$C_6H_5-CH(O-(CH_2)_2-N(CH_2)_5)-CO-NR^1R^2 = C_{15}H_{20}N_2O_2R^1R^2$

R^1	R^2	Yield, %	M. p.,[a] °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Antispas.[b] 1	Antispas.[b] 2
H	H	165–167	155–157	10.69	10.77	20	80
CH_3	H	51	133–134	10.15	10.26	15	10
C_6H_5	H	43	171–172	6.39	6.48		
C_2H_5	C_2H_5	47	[c]	8.80	8.91		

[a] Corrected. [b] Tests as given in Table I. [c] An oily solid that melted slightly above room temperature.

Summary

Six dialkylaminoalkyl α-(2-dialkylaminoalkoxy)-phenylacetates have been prepared and characterized. In addition six N- and N,N-disubstituted α-bromophenylacetamides have been synthesized and four of these converted to the corresponding N- and N,N-substituted α-(2-piperidinoethoxy)-phenylacetamides. A partial evaluation of the physiological properties for some of these compounds is given.

DENTON, TEXAS

RECEIVED MARCH 25, 1949

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

Synthesis of Certain 2-Alkoxyethyl Phenyl Ketones[1]

BY ROBERT EDWARD LESLIE[2] AND HENRY R. HENZE

In connection with another problem, certain alkoxyethyl ketones, especially the 2-propoxyethyl phenyl and 2-(1-methylethoxy)-ethyl phenyl ketones, were needed. Initially, it was visualized that these ketones might be prepared from interaction of Grignard reagents and appropriately substituted alkoxypropionitriles. Attempts to develop this method were not successful, but the desired substances were obtained as a result of reactions between diphenylcadmium and certain β-alkoxypropionyl chlorides. The latter were synthesized through the following sequence: (a) addition of appropriate alcohols to acrylonitrile[3] forming β-alkoxynitriles; (b) hydrolysis of the latter to the corresponding β-alkoxypropionic acids; (c) subsequent conversion into β-alkoxypropionyl chlorides.

Preparation of the ketones was tried first by the method of Cason,[4] namely, addition of the acyl halide to the solution of diphenylcadmium, but the reaction complexes formed very heavy precipitates. Before reaction was complete, agglutination of the suspended matter made stirring practically impossible and thus homogenization of the reaction mixtures was not attained. However, by reversing the sequence of addition of reactants, clumping of the addition products was avoided and

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[1] From the M.A. thesis of R. E. Leslie, June, 1948.

[2] Present address: Guatemala City, Guatemala, C. A.

[3] Utermohlen, THIS JOURNAL, **67**, 1505 (1945).

[4] Cason, *ibid.*, **68**, 2078 (1946).

TABLE I

β-ALKOXYPROPIONIC ACIDS R—O—CH_2CH_2COOH

—R	B. p., °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	Equiv. wt. Calcd.	Found	Molec. refraction Σ	Calcd.
C_2H_5	107	10	58	1.4216	1.1490	118.1	118.2	28.47	28.54
C_3H_7	117	8	65	1.4238	1.0148	132.2	134.1	33.09	33.20
$CH(CH_3)_2$	101	4	62	1.4208	1.0074	132.2	137.9	33.09	33.25
C_4H_9	112	3	55	1.4280	0.9908	146.2	146.2	37.70	37.95

the yields of ketones were increased. It was found preferable, also, to use ether as the solvent and diluent, rather than to employ benzene, as described by Cason. Five β-alkoxyethyl phenyl ketones (alkyl = CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$ and C_4H_9) were prepared.

Experimental

Preparation of β-Propoxypropionitrile.[4a]—One hundred and seventy grams of acrylonitrile was added dropwise to a solution of 3 g. of sodium methoxide in 120 g. of propanol with maintenance of the temperature below 70°. Two hundred five grams (77% yield) of product was obtained; b. p. 92° (24 mm.), $n^{20}D$ 1.4128, d^{20}_4 0.8969, Σ *MR* 31.30, *MR* calcd. 31.44.

Preparation of β-Alkoxypropionic Acids.—In general, one mole of a β-alkoxypropionitrile was added slowly dropwise with stirring to 50 ml. of 75–80% sulfuric acid, resulting in the formation of a homogeneous solution. The latter, with stirring, was heated for approximately ten minutes at which time a sudden increase in the rate of reflux was observed.[5] Heating was discontinued for twenty minutes, then 60 ml. of water was added and the mixture was subjected to gentle warming, at the reflux temperature, and stirring for ninety minutes longer. The reaction mixture was cooled, the organic layer was removed and added with stirring to a cooled solution of one mole of sodium hydroxide in 300 ml. of water. Upon cooling, the insoluble, upper layer of organic material was removed. The lower layer was acidified, and the additional organic matter which separated was added to the previously collected main fraction of the alkoxy acid. The crude product was dried over anhydrous sulfate before fractionation *in vacuo*. Data obtained for these four acids are listed in Table I.

Preparation of β-Alkoxypropionyl Chlorides.—The acid (1 mole) was added dropwise to the stirred thionyl chloride (1.5 moles) which was warmed since the reaction was notably endothermic. After stirring the mixture for one hour without further heating, the material was fractionated *in vacuo*. Certain data concerning the five acid chlorides prepared are given in Table II.

TABLE II

β-ALKOXYPROPIONYL CHLORIDES R—O—$CH_2CH_2CO{\cdot}Cl$

—R	B. p., °C.	Mm.	Yield, %	d^{20}_4	Chlorine, % Calcd.	Found[a]
CH_3[b]	64	44	85	1.1256	28.92	29.03
C_2H_5	77.5	52	96	1.0594	25.97	26.10
C_3H_7	77	25	92	1.0424	23.53	23.58
$CH(CH_3)_2$	73.5	30	91	1.0343	23.53	23.82
C_4H_9	86	20	94	1.0157	21.53	21.62

[a] Weighed sample was warmed with dilute sodium hydroxide solution before completing the gravimetric analysis. [b] The sample of β-methoxypropionic acid was donated by The B. F. Goodrich Co., Akron, Ohio.

Preparation of 2-Alkoxyethyl Phenyl (or Alkyl) Ketones.—One-fourth mole of β-ethoxypropionitrile in 250 ml. of anhydrous ether was added dropwise with stirring to a solution of three-fourths mole of ethylmagnesium bromide in 550 ml. of ether. The evolution of heat was quite noticeable, and a dark green precipitate separated from solution. A small sample of the addition-product was removed and dried to yield a very fine yellow powder which reacted vigorously with water to form a yellow gum. Upon treatment of the small sample with water, ammonia was evolved. Hydrolysis of the main portion was attempted with ice-cold hydrochloric acid; an insoluble, red gum resulted. From the ether solution, upon distillation, there was obtained only a small volume of low-boiling liquid which failed to exhibit typical ketone function. The red gum, also, failed to give a carbonyl test. After fusion of the gummy material with sodium, tests for the presence of magnesium and chlorine were positive, but for nitrogen was negative.

The attempted preparation of a ketone was repeated, except that the solution of ethylmagnesium bromide was added to that of β-ethoxypropionitrile. Similar results were obtained.

A solution of β-methoxypropionitrile in ether was added to a very dilute ether solution of phenylmagnesium bromide (4 equivalents); reaction was vigorous, a viscous gummy mass was formed and was treated with ice-cold, concentrated hydrochloric acid. Again, no identifiable product was isolated.

A similar negative result was obtained when β-ethoxypropionitrile in butyl ether was added to 2.5 equivalents of phenylmagnesium bromide in butyl ether solution.

Attempts were then made to prepare alkoxyethyl phenyl ketones using Cason's procedure.[4] Phenylmagnesium bromide, in 6–7 volumes of absolute ethyl ether, was treated with finely divided, anhydrous cadmium chloride; heat was evolved, the solution darkened in color and suspension of a white precipitate was noted. After addition of the cadmium chloride was complete, usually in five to ten minutes, the reaction mixture was stirred for ninety minutes. Upon discontinuing the stirring, the mixture separated into three layers; the two upper, liquid layers were decanted into a separatory funnel for dropwise addition to the appropriate β-alkoxypropionyl chloride diluted with 5–6 volumes of anhydrous benzene. An approximate ratio of 0.6 mole (estimated) of diphenylcadmium to 1 mole of acyl chloride was employed. As the reactions were exothermic, cooling of the mixture was necessary. A gray precipitate formed and was in such finely divided condition as to offer little resistance to the stirrer. Stirring was continued for one hour.

The mixture was hydrolyzed with ice-cold, concentrated hydrochloric acid. Initially a gray, viscous gum formed, but disappeared after about five minutes, and a clear upper layer formed and was separated. After removal of ether and benzene, the organic material was washed with an aqueous solution of sodium bicarbonate, dried over anhydrous calcium chloride, subjected to a pressure of 4 mm. at room temperature before being distilled at less than 1 mm. pressure. Unless distilled at this low pressure the ketones tended to decompose forming acrylophenone and the corresponding alcohols. Data, secured from characterization of the ketones, have been placed in Table III.

[4a] After completion of all the Experimental and after deposit of the M.A. thesis (March, 1948), Christian and Hixon (THIS JOURNAL, **70**, 1333 (1948)) reported the synthesis in 84% yield of β-propoxypropionitrile; b. p. 84° (19 mm.), $n^{20}D$ 1.4131, d^{20}_{20} 0.9006.

[5] In hydrolysis of β-alkoxypropionitriles by the action of concentrated sulfuric acid, precaution needed to be taken so as to avoid excessive heating in the preliminary course of the reaction. The reaction is so exothermic as to be difficult to control. Overheating resulted in loss of material and possibly could bring about personal injury.

TABLE III

2-ALKOXYETHYL PHENYL KETONES $R—O—CH_2CH_2COC_6H_5$

—R	Yield, %	n^{20}_D	d^{20}_4	Molec. refrac. Σ	Molec. refrac. Calcd.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3[a]	90	1.5250	1.0602	46.96	47.46	73.14	73.12	7.37	7.36
C_2H_5[b]	82	1.5190	1.0356	51.57	52.23	74.13	73.93	7.92	7.73
C_3H_7	82	1.5193	1.0300	56.19	56.68	74.97	74.30	8.39	7.83
$CH(CH_3)_2$	89	1.5083	1.0108	56.19	56.73	74.97	74.39	8.39	8.30
C_4H_9	91	1.5036	0.9976	60.81	61.19	75.69	74.98	8.80	8.78

[a] Straus and Berkow (ref. 7, p. 144) reported b. p. 125–126° (16 mm.), d^{15}_4 1.020. [b] Kohler (ref. 6, p. 388), who obtained this ketone as a by-product in the preparation of phenyl vinyl ketone from α,β-dibromopropiophenone, reported b. p. 135° (18 mm.), m. p. about 12°.

These alkoxyethyl phenyl ketones readily formed 2,4-dinitrophenylhydrazones; the melting points of the latter are given in sequence to the appropriate alkyl group: CH_3, 175.5–176.5°; C_2H_5, 161.0–161.5°; C_3H_7, 158.0–158.5°; $CH(CH_3)_2$ 174.5–175.0°; C_4H_9, 152.5–153.0°.

In one instance, the impure 2-(1-methylethoxy)-ethyl phenyl ketone, obtained by distillation as described above, was redistilled through a six-inch column from an oil-bath at 140–155°. Several fractions of constant refractive index were removed at 106–107° (18 mm.)[6,7] and were found to possess the following physical properties: n^{20}_D 1.5440; d^{20}_4 1.0350; ΣMR[8] 40.35; MR calcd. 40.31. The product, acrylophenone, formed (a) a 2,4-dinitrophenylhydrazine derivative [or 1-(2,4-dinitrophenyl)-3-phenyl-Δ^2-pyrazoline], m. p. 155–156° and (b) a phenylhydrazine derivative [or 1,3-diphenyl-Δ^2-pyrazoline],[9,10,11] m. p. 153°.

Summary

1. Certain β-alkoxypropionitriles, obtained by the interaction of acrylonitrile and various alcohols, were hydrolyzed to yield β-alkoxypropionic acids which, in turn, were converted into the corresponding acid chlorides.

2. The β-alkoxypropionyl chlorides reacted with diphenylcadmium to yield 2-alkoxyethyl phenyl ketones, three of which have not previously been reported. These ketones tend to be unstable upon distillation and decompose to produce acrylophenone.

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(6) Kohler, *Am. Chem. J.*, **42**, 375 (1909), reported b. p. 118° (18 mm.).

(7) Straus and Berkow, *Ann.*, **401**, 121 (1913), reported b. p. 115° (18 mm.).

(8) Includes 0.65 correction for exaltation of C_6H_5CO– compounds; *cf.* Auwers, *Ber.*, **45**, 2765 (1912).

(9) Straus and Berkow, ref. 7, reported m. p. 152°.

(10) Schafer and Tollens, *Ber.*, **39**, 2181 (1906), reported m. p. 152–153°.

(11) Young and Roberts, THIS JOURNAL, **68**, 649 (1946), reported m. p. 154–155°.

AUSTIN, TEXAS RECEIVED FEBRUARY 19, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

A Proposed Mechanism of the Alkylation of Benzyl Halides with Nitro Paraffin Salts[1]

BY H. B. HASS[2] AND MYRON L. BENDER[3]

It was shown in the preceding paper[4] that, of nine para-substituted benzyl halides, only *p*-nitrobenzyl chloride gave carbon-alkylation with sodium 2-propanenitronate whereas the other eight benzyl halides gave oxygen-alkylation in 68–77% yield as illustrated in the equations

$$p\text{-}NO_2C_6H_4CH_2Cl + (CH_3)_2CNO_2^-Na^+ \longrightarrow p\text{-}NO_2C_6H_4CH_2C(CH_3)_2NO_2$$

$$p\text{-}CH_3C_6H_2CH_2Br + (CH_3)_2CNO_2^-Na^+ \longrightarrow p\text{-}CH_3C_6H_4CHO + (CH_3)_2C{=}NOH$$

These facts led us to seek some explanation for the anomalous behavior of *p*-nitrobenzyl chloride in this reaction.

The anions of nitroparaffin salts have been represented as resonance hybrids involving forms with the negative charge on oxygen or on carbon.[5] Carbon-alkylation may then be considered[6] to involve a nucleophilic displacement by the resonating anion at carbon while oxygen-alkylation may be considered to involve a displacement by the resonating anion at oxygen. The compounds resulting from oxygen-alkylation, nitronic esters, have been isolated in several cases similar to the present work[7] and have been prepared by a different synthesis[8]; they are thermally instable and decompose spontaneously even at room temperature into carbonyl compounds and oximes. While the mechanisms discussed above account for the possibility of the two modes of alkylation, they furnish no basis of explaining the anomalous behavior of *p*-nitrobenzyl chloride.

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(1) An abstract of a thesis by Myron L. Bender, submitted to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1948. Presented before the Division of Organic Chemistry, 114th American Chemical Society meeting, St. Louis, Missouri, September 6, 1948.

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(4) Hass and Bender, THIS JOURNAL, **71**, 1767 (1949).

(5) Kornblum, Lichtin, Patton and Iffland, *ibid.*, **69**, 307 (1947).

(6) Hauser, *ibid.*, **60**, 1957 (1938).

(7) Thurston and Shriner, *J. Org. Chem.*, **2**, 183, 560 (1937–1938); Weisler and Helmkamp, THIS JOURNAL, **67**, 1167 (1945), and other references cited therein.

(8) Arndt and Rose, *J. Chem. Soc.*, 1 (1935).