and acidification the light yellow precipitate of crude β-(4-methoxy-1-naphthoyl)-propionic acid which formed was separated by filtration and crystallized from methanol (Norite). The product was collected on a filter and recrystallized from methanol. Observed melting points when the melting point tubes were placed in the bath at 160° were: 171.5–172° and 174–174.5° (reported m. p. 171°,[8] 172°,[9] 177–178°[5]). The yield was 1.86 g. (20.7%) based upon the amine hydrochloride.

4-Methoxy-1-naphthoic Acid. (1) **Hypochlorite Oxidation of β-(4-Methoxy-1-naphthoyl)-propionic Acid.**—One gram of β-(4-methoxy-1-naphthoyl)-propionic acid was dissolved in 100 ml. of freshly prepared sodium hypochlorite solution (made by dissolving 5.8 g. of sodium hydroxide in 100 ml. of water and adding 1.8 g. of chlorine to the solution); this solution was approximately 0.25 *N* with respect to sodium hypochlorite and 0.5 *N* with respect to sodium hydroxide. The mixture was heated gently in a water-bath (80–82°) for twenty minutes, boiled under reflux on a sand-bath for twenty minutes, allowed to cool slightly and was filtered. Sulfur dioxide was bubbled into the cooled filtrate until the solution was acid to congo red paper. The white solid which deposited was separated on a filter, and thoroughly washed with water. The precipitate was crystallized twice from methanol, m. p. 236–239° (inserted into the bath at 220°). The compound darkened upon melting and bubbles of gas appeared (reported, 230°,[10] 232°,[11] 234°,[8] 239°,[12] and 242–243°[13]). The yield was 0.16 g. (20.5%).

(2) **Hypochlorite Oxidation of 4-Methoxy-1-acetonaphthone.**—To a solution of 1 g. of 4-methoxy-1-acetonaphthone[14] in 10 ml. of methanol, 35 ml. of "Chlorox" (5.25% by weight of sodium hypochlorite) was added slowly in small portions at room temperature over a thirty minute period. After the addition of all the sodium hypochlorite solution, 10 ml. of methanol was added. After heating the solution for forty minutes (as above), a dark yellow layer which had formed at the bottom of the flask was removed by extraction with ether and discarded. The product was isolated from the aqueous layer, using the procedure given in the preceding preparation, and was recrystallized from methanol; m. p. 236–240° (inserted into the bath at 220°). The compound darkened upon melting and bubbles of gas appeared.

A mixed melting point of the hypochlorite oxidation products of β-(4-methoxy-1-naphthoyl)-propionic acid and 4-methoxy-1-acetonaphthone showed no melting point depression. The infrared absorption spectra of the two compounds were identical; both showed very strong absorption at 1677 cm.$^{-1}$, 1268 cm.$^{-1}$ and 768 cm.$^{-1}$.[15]

(8) Ruzicka and Waldman, *Helv. Chim. Acta*, **15**, 907 (1932).
(9) Fieser and Hershberg, THIS JOURNAL, **58**, 2316 (1936).
(10) Rousset, *Bull. soc. chim.*, [3] **17**, 309 (1897).
(11) Gattermann and Hess, *Ann.*, **244**, 73 (1888).
(12) Herz, Schulte and Zerweck, U. S. Patent 1,669,297, May 8, 1928; *C. A.*, **22**, 2170 (1928).
(13) Spaith, Geissman and Jacobs, *J. Org. Chem.*, **11**, 399 (1946).
(14) Witt and Braun, *Ber.*, **47**, 3219 (1914).
(15) The authors are indebted to Mrs. A. Johnson for the interpretation of the infrared spectra.

URBANA, ILLINOIS RECEIVED DECEMBER 3, 1948

Summary

The succinoylation of 1-acetylamino-6-methoxynaphthalene in nitrobenzene in the presence of aluminum chloride at 0° gave β-(2-methoxy-5-acetylamino-1-naphthoyl)-propionic acid.

The succinoylation of 1-acetylamino-8-methoxynaphthalene in nitrobenzene in the presence of aluminum chloride at 0° gave β-(4-methoxy-5-acetylamino-1-naphthoyl)-propionic acid.

No other isomers were found in either instance.

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

Synthesis of 1-Methoxypropyl Ketones[1]

BY HENRY R. HENZE, GEORGE W. BENZ AND GEORGE L. SUTHERLAND

It has been demonstrated that many, although not all, ketones can be converted into 5,5-disubstituted hydantoins by means of the Bucherer method[2] or through the improvements upon the latter developed by Henze and Long.[3] Since a series of 5-alkoxymethyl-5-phenylhydantoins has been shown[4] to possess a high degree of anticonvulsant activity, the latter varying with the degree of branching at the α-carbon of the alkoxy group, it was desirable to prepare isomeric and homologous ketones for subsequent conversion, if possible, into hydantoin derivatives.

The present investigation dealt with the synthesis of fifteen 1-methoxypropyl ketones. With respect to the other grouping present in these mixed ketones, six are straight chain alkyl, seven are branched chain alkyl, one is cycloalkyl, and one is phenyl. These ketones resulted from a sequence of steps: (a) preparation of 1-chloropropyl methyl ether; (b) conversion of the latter into 1-methoxybutyronitrile; (c) interaction of the alkoxynitrile with appropriate Grignard reagents to yield the keto ethers.

(1) From the M.A. thesis of G. W. B., August, 1946, and of G. L. S., August, 1947.
(2) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).
(3) Henze and Long, THIS JOURNAL, **63**, 1936, 1941 (1941).
(4) Henze, Melton and Forman, *ibid.*, **70**, 2438 (1948); Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

Experimental

Preparation of 1-Chloropropyl Methyl Ether.—This chloro ether was prepared according to the method of Henry[5] by saturating with dry hydrogen chloride a well-stirred mixture of methanol (224 g., 7 moles) and propionaldehyde (406 g., 7 moles) in a container chilled by a salt-ice-bath. After about six hours, the two-phase mixture was separated, the top (chloro ether) layer was dried over anhydrous calcium chloride in a refrigerator, and was fractionated. After removal of about 110 g. of lower boiling material, there was collected 250 g. (33% yield) of material boiling through the range 96–108° (747 mm.).

The chloro ether could not be preserved without evidence of decomposition; hence, was converted as soon as possible to the alkoxy nitrile, which can be purified readily through fractional distillation.

Preparation of 1-Methoxybutyronitrile.—The procedure most commonly employed for the conversion of α-chloro ethers into the corresponding alkoxynitriles is that of

(5) Henry, *Compt. rend.*, **100**, 1007 (1885).

TABLE I

1-METHOXYPROPYL ALKYL (OR CYCLOHEXYL OR PHENYL) KETONES, $CH_3CH_2CH(OCH_3)—CO—R$

-R	Boiling range °C.	Mm.	Micro b. p., °C.	Mm.	Yield, %	n_D^t	d_4^t	Mol. refraction Summation	Mol. refraction Calcd.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$-CH_3$	70–71	95	109	747	29	1.4015[a]	0.8963[a]	31.56	31.52	62.04	61.88	10.41	10.69
$-C_2H_5$	62–63	40	112	741	79	1.4080[a]	.8902[a]	36.18	36.09	64.57	64.34	10.84	11.01
$-C_3H_7$	85–86	42	134	746	69	1.4131[a]	.8832[a]	40.80	40.73	66.63	66.53	11.18	11.45
$-CH(CH_3)_2$	65–66	23	133	748	44	1.4159[b]	.8847[b]	40.80	40.89	...	66.62	...	11.34
$-C_4H_9$	84–86	20	153	741	53	1.4181[a]	.8777[a]	45.42	45.41	68.31	68.07	11.47	11.41
$-CH(CH_3)C_2H_5$	80–82	20	183	748	38	1.4247[b]	.8879[b]	45.42	45.53	...	68.08	...	11.43
$-CH_2CH(CH_3)_2$	80–82	17	181	749	65	1.4218[b]	.8733[b]	45.42	45.59	...	68.66	...	11.47
$-C_5H_{11}$	109–113	29	190	750	31	1.4224[a]	.8765[a]	50.03	49.96	69.72	69.91	11.70	11.64
$-CH(CH_3)C_3H_7$	94–96	22	194	746	50	1.4273[b]	.8866[b]	50.03	49.92	...	69.63	...	12.05
$-CH_2CH(CH_3)C_2H_5$	104–106	30	204	748	17	1.4[illegible][b]	.8836[b]	50.03	50.57	...	70.00	...	11.81
$-C_2H_4CH(CH_3)_2$	99–101	26	194	747	54	1.4243[b]	.8742[b]	50.03	50.13	...	69.59	...	11.53
$-CH(C_2H_5)_2$	106–108	30	186	744	27	1.4298[b]	.8932[b]	50.03	50.09	...	69.25	...	11.38
$-C_6H_{13}$	123–127	29	192	746	65	1.4261[a]	.8751[a]	54.65	54.57	70.92	70.91	11.90	12.17
$-C_6H_{11}$[d]	129–130	30	233	748	38	1.4574[b]	.9462[b]	52.47	52.42	71.69	72.00	10.94	11.18
$-C_6H_5$	139–141	28	204	744	56	1.5125[a]	1.0291[a]	51.70[c]	52.01	74.13	73.94	7.92	7.87

[a] t, 25°. [b] t, 20°. [c] Includes 0.65 exaltation for benzoyl group, *cf.* Auwers, *Ber.*, **45**, 2765 (1912). [d] Cyclohexyl group.

Gauthier[6] in which the chloro compound is warmed with cuprous cyanide. When such a mixture, diluted with anhydrous benzene, was heated to refluxing for about three and one-half hours and was filtered, the filtrate upon fractionation yielded no significant amount of the desired product.

An attempt was made to obtain the nitrile by interaction of 168 g. of the partially purified chloro ether in benzene solution with 427 g. of mercuric cyanide; the period of refluxing was twelve hours. After filtration of the reaction mixture, fractionation of the filtrate yielded material which required redistillation. Using a twelve inch column, packed with glass helices, there was obtained 24 g. (17% yield) of the desired compound; b. p. 130–132° (748 mm.); $n^{25}D$ 1.3918; d^{25}_4 0.8828; ΣMR 26.68; MR calcd. 26.73.

Anal. Calcd. for C_5H_9NO: N, 14.13. Found: N, 13.98.

The most satisfactory preparation of the desired nitrile resulted from the dropwise addition, in the course of thirty minutes, of 250 g. (2.3 moles) of once-distilled α-chloropropyl methyl ether onto a well-stirred suspension of 300 g. (2.2 moles) of silver cyanide in 500 ml. of decalin. The heat of reaction was sufficient to cause refluxing of the solution; however, the mixture was heated on a water-bath for about twelve hours.

After filtering off the salts and washing them with decalin, the decalin solution was distilled and all material boiling up to 165° was collected. The distillate was fractionated through the twelve-inch, packed column and 115 g. (52% yield) of product, boiling at 130–135° (746 mm.), was obtained. A small portion of the 1-methoxybutyronitrile was redistilled before analysis; b. p. 133° (746 mm.); $n^{25}D$ 1.3928; d^{25}_4 0.8835; ΣMR 26.68; MR calcd. 26.67.

Anal. Calcd. for C_5H_9NO: C, 60.58; H, 9.15. Found: C, 60.68; H, 9.24.

In an attempt to repeat this preparation in strict duplication of quantities and conditions, the nitrile was obtained in a yield of but 25.4%; $n^{20}D$ 1.4025; d^{20}_4 0.9051; ΣMR 26.68; MR calcd. 26.69.

Synthesis of 1-Methoxypropyl Alkyl (Cyclohexyl or Phenyl) Ketones.—Using the Behal and Sommelet[7] adaptation of Blaise's[8] method for production of alkoxy ketones, the alkoxynitrile was added to 3–4 equivalents of the appropriate Grignard reagent with subsequent hydrolysis of the addition product. In general, the alkyl halides were bromides (with exception of methyl iodide) and were the best grade obtainable from Eastman Chemical Company, Paragon Testing Laboratories or Columbia Organic Chemicals Company. However, 3-bromopentane was synthesized from interaction of phosphorus tribromide and authentic 3-pentanol (produced from hydrolysis of the addition product formed from action of ethylmagnesium bromide upon propionaldehyde). Likewise, 1-bromo-2-methylbutane was prepared from 2-methyl-1-butanol resulting from hydrolysis of the formaldehyde addition product of 1-methylpropylmagnesium bromide.

In all cases save one, the alkoxynitrile was added slowly to the filtered Grignard reagent solution; in making amyl 1-methoxypropyl ketone, the Grignard reagent solution was added to the nitrile. After hydrolysis of the addition product with diluted hydrochloric acid, the layer containing the ketone was dried over anhydrous calcium chloride. The ketones were fractionated under diminished pressure.

TABLE II

SEMICARBAZONES OF 1-METHOXYPROPYL ALKYL (OR CYCLOHEXYL OR PHENYL) KETONES

$$CH_3CH_2CH(OCH_3)—C(R)=NNHCONH_2$$

-R	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_3$	146–147	24.26	24.55
$-C_2H_5$	144–145	22.44	22.57
$-C_3H_7$	156.5–157.0 dec.	20.88	20.87
$-CH(CH_3)_2$	134–136	20.88	20.98
$-C_4H_9$	152–153	19.51	19.66
$-CH(CH_3)C_2H_5$	91–92	19.51	19.45
$-CH_2CH(CH_3)_2$	152–154	19.51	19.52
$-C_5H_{11}$	106–107	18.33	18.52
$-CH(CH_3)C_3H_7$	80[a]		
$-CH_2CH(CH_3)C_2H_5$	99–100	18.33	18.61
$-C_2H_4CH(CH_3)_2$	131–133	18.33	18.10
$-CH(C_2H_5)_2$	93[a]		
$-C_6H_{13}$	101–103	17.27	17.29
$-C_6H_{11}$[b]	147–149	17.41	17.70
$-C_6H_5$	90–91	17.86	17.89

[a] Partially purified product, initially separated as a liquid which subsequently solidified. [b] Cyclohexyl.

(6) Gauthier, *ibid.*, **143**, 831 (1906).

(7) Behal and Sommelet, *ibid.*, **138**, 89 (1904).

(8) Blaise, *ibid.*, **132**, 38 (1901).

Data for some properties of these ketones have been collected in Table I. From these ketones were prepared semicarbazones,[9] for which melting points and analytical data are reported in Table II. Even though a much longer period of heating than usual was employed, it was difficult to obtain, even in poor yield, semicarbazones from the 1-methylbutyl and 1-ethylpropyl ketones. Purification of the semicarbazones also was difficult in these two cases.

From time to time attempts have been made in this Laboratory to regenerate ketones from semicarbazones, or similar derivatives, as a means of purification of alkoxyalkyl alkyl (or phenyl) ketones. In general, these attempts have been unsuccessful. However, by adding dropwise a saturated solution of sodium nitrite[10] to an ice-cold, glacial acetic acid solution of the semicarbazone of 1-methoxypropyl 3-methylbutyl ketone, then warming the mixture for ten minutes before pouring into ten volumes of water, there was obtained a sparingly soluble layer. The latter was dried and distilled to yield the ketone in 63% yield.

(9) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 142.

Summary

Fifteen ketones have been synthesized by interaction of appropriate Grignard reagents with 1-methoxybutyronitrile.

(10) Goldschmidt and Veer, *Rec. trav. chim.*, **65**, 796 (1946).

AUSTIN, TEXAS RECEIVED FEBRUARY 7, 1949

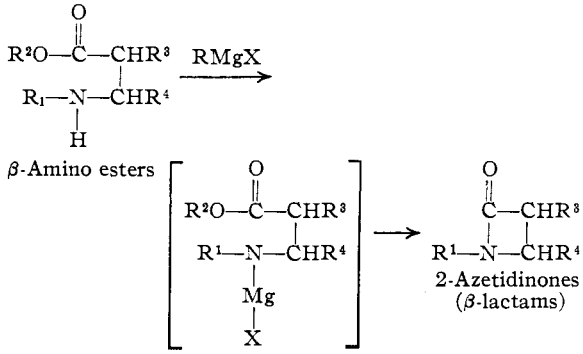
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE STATE COLLEGE OF WASHINGTON]

Synthesis and Reactivity of Some 1-Alkyl-2-azetidinones (N-Alkyl-β-lactams)[1]

BY ROBERT W. HOLLEY[2,3] AND ANN D. HOLLEY[3]

The discovery that the reactive ring system present in the penicillins is probably a β-lactam[4] has greatly stimulated interest in β-lactams and has made the relation of reactivity of β-lactams to their structure a problem of considerable importance. β-Lactams known prior to the war-time penicillin work were found to be relatively resistant to hydrolysis, behavior which is characteristic of most amides. A number of different β-lactams were prepared and studied during the penicillin work and data concerning them is summarized in "The Chemistry of Penicillin."[5] The number of synthetic methods for the preparation of β-lactams is still very limited, however, and the data on their reactivity are inadequate for a conclusion to be drawn as to the reason for the reactivity of the penicillins.

The reaction of a β-amino ester with a Grignard reagent, according to the following equation, was one of the methods developed for the synthesis of β-lactams during the war-time penicillin work.[5] Presumably an intermediate aminomagnesium halide is formed; the reaction of aminomagnesium halides with esters is known to afford amides.[6] Five β-lactams, all with N-phenyl substitution ($R^1 = C_6H_5$) had been prepared by this method.[5]



The present study was undertaken to determine the applicability of this reaction to the synthesis of N-alkyl-β-lactams and, if possible, to find a relationship between the yield of β-lactam and the structure of the β-amino ester used in the reaction.

Four N-alkyl-β-lactams were subsequently synthesized: 1-methyl-2-azetidinone, I, $R^1 = CH_3$, $R^3 = R^4 = H$; 1-benzyl-2-azetidinone, II, $R^1 = C_6H_5CH_2$, $R^3 = R^4 = H$; 1-benzyl-4-phenyl-2-azetidinone, III, $R^1 = C_6H_5CH_2$, $R^3 = H$, $R^4 = C_6H_5$; 1-benzohydryl-4-phenyl-2-azetidinone, IV, $R^1 = (C_6H_5)_2CH$, $R^3 = H$, $R^4 = C_6H_5$. Some reactions of these four β-lactams were studied, and particular attention was given to the relationship of structure to reactivity.

Synthesis of N-Alkyl-β-lactams

Each of the four β-amino esters used was subjected to identical reaction conditions. An aliquot of the crude organic material from each reaction was titrated with hydrochloric acid, and from the neutralization equivalent found, the per cent. of amino ester units [$R^1NH - - - CH(R^4)CH_2CO_2C_2H_5$] remaining was calculated. By difference, the amount of amide [$-CH(R^4)CH_2CON(R^1)-$] present in the material and the percentage yield of amide were determined; the latter is given in

(1) This work was supported in part by a grant from the College Committee on Research of The State College of Washington.

(2) American Chemical Society Postdoctoral Fellow, 1947-1948.

(3) Present address: New York State Agricultural Experiment Station, Geneva, N. Y.

(4) Committee on Medical Research, O. S. R. D., *Science*, **102**, 627 (1945).

(5) S. A. Ballard, D. S. Melstrom and C. W. Smith, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, Chap. XXVI.

(6) F. Bodroux, *Compt. rend.*, **138**, 1427 (1904).