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Monocarbamates of 1,2-Dihydroxy-3-aryloxypropanes

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Ester interchange between diethyl carbonate and 1,2-dihydroxy-3-aryloxypropanes produces high yields of dioxolones which on treatment under mild conditions with ammonia in an alcohol give good yields of the carbamate of the primary alcohol group. In one case (Compound If) the isomeric carbamate (of the secondary alcohol group) was isolated from mother liquors and also synthesized by an unequivocal independent synthesis.

The rearrangement of derivatives of a-hydroxycarbamates is discussed. A method is provided for converting secondary carbamates to primary carbamates.

Monocarbamates of 1,2-dihydroxy-3-aryloxypropanes have recently emerged as a therapeutically useful group of compounds.²⁻⁴ The presently most important members of this group have been formulated as Ia although no rigorous proof was presented that they are indeed Ia rather than their structural isomers Ib.



This investigation was undertaken in order to provide a satisfactory practical method for preparing the carbamates Ia and to determine by independent unequivocal synthesis whether the previous structural assignments have been correct.

Our results, reported here, are a new synthesis of Ia that is suitable for manufacturing purposes and a confirmation of the structure disclosed for the monocarbamate of 1,2-dihydroxy-3-(o-methoxyphenoxy) propane (Ie).⁴ In addition we have discovered a hitherto unnoted rearrangement of carbamates Ie and If.

Synthesis. Monocarbamates of 1,2-dihydroxy-3aryloxypropanes (Ic) have been prepared^{2,4} by treating a solution of Ic with one mole of phosgene. which was assumed⁵ to react preferentially with the primary alcohol group to yield the hydroxychlorocarbonates (Id) (not isolated); the latter were then converted by aqueous ammonia to Ia. Alterna-

(4) R. S. Murphey (to A. H. Robins Co., Inc.), U. S. Patent 2,770,649, Nov. 13, 1956.

(5) Reference (2), footnote 8.

tively.⁶ Ic was treated with phosgene under more severe conditions than above to yield the cyclic carbonate (or dioxolone) II, which, upon reaction





with liquid ammonia, yielded the same monocarbamate as was obtained via the chlorocarbonate route.

We have found that the dioxolones II are obtained in very high yield by ester interchange between Ic and diethyl carbonate in the presence of a catalytic amount of a metallic alkoxide.⁷ The alkoxide may be added from an external source or may be formed in situ, e.g., by dissolving sodium in molten Ic. Upon completion of the ester interchange, the alkoxide is destroyed by the addition of ammonium chloride and the excess diethyl carbonate is recovered by distillation. The residual crude cyclic carbonate is suspended in a suitable solvent (such as ethyl or isopropyl alcohol), ammonia gas is introduced, the system is closed and the mixture is stirred at room temperature for 8-16 hours. After the first several hours, the initial precipitate disappears and thereafter the somewhat turbid solution begins to deposit crystals copiously. Excess ammonia is expelled by heating, and from the cooled clarified solution⁸ the crude product (60-80%) yield) is recovered by filtration. Recrystallization from alcohols or ethyl acetate yields 60-65% of pure Ia.

(6) B. J. Ludwig and E. C. Piech, J. Am. Chem. Soc., 73, 5894 (1951).

(7) Other catalysts such as anhydrous potassium carbonate (cf. M. S. Morgan and L. H. Cretcher, J. Am. Chem. Soc., 68, 783 (1946)) are also effective.

(8) An aliquot of the solution was taken to dryness in vacuo. The weight of the residue indicated quantitative conversion to monocarbamates. A sample of the residue was analyzed by Dr. Eric Smith, S. B. Penick and Co., using infrared spectroscopy and was found to contain 70-73% of Ie. All other infrared data reported here were likewise obtained by Dr. Smith.

⁽¹⁾ We wish to thank Dr. W. G. Bywater, S. B. Penick and Co., for reviewing this paper

⁽²⁾ H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim, and W. A. Lott, J. Am. Chem. Soc., 72, 3710 (1950).
(3) New and Nonofficial Remedies," J. B. Lippincott

Co., 1956, p. 467.

The results of the ammonolysis of IIa were studied in detail. From the mother liquors remaining after the removal of pure Ie, melting in the range 93-97°, there was obtained by careful fractional crystallization, preferably from ethyl acetate, a quantity of isomeric carbamate, m.p. 117-119°, shown below to have the structure If. The highermelting isomer was always obtained in minor yield, but its formation was not suppressed by conducting the ammonolysis at higher or lower temperatures or under pressure.⁹

The infrared spectrum of If differs substantially from that of Ie in the "fingerprint region." In particular If has a very strong absorption band at 10.17 μ which is completely absent in the spectrum of Ie.

Structural Investigation. As mentioned above, the reaction of one mole of phosgene with Ic was assumed to take place at the primary alcohol group and to lead from the chlorocarbonate to the primary monocarbamate. In order to confirm this structure, the synthesis of If pictured in Chart I was carried out.



V was prepared by either of two routes: (a) by condensation of epichlorohydrin with sodium benzylate followed by reaction of the resultant epoxide with guaiacol in the presence of a small amount of base;¹⁰ (b) by condensation of Marle's chlorohydrin IV^{10} with sodium benzylate. Route (b) gave the better yield of V. The identity of V from either source was verified by comparison of the refractive indices of the alcohols and the melting points and mixture melting points of the *p*-nitrobenzoates. Phosgenation of V followed by reaction of the unisolated intermediate chlorocarbonate with ammonia gave the benzyloxycarbamate VI. Hydrogenolysis in isopropyl alcohol at room temperature and atmospheric pressure led to VII, identical in melting point and infrared spectrum with If. The lower melting isomer is therefore the primary carbamate Ie as previously formulated.

Rearrangements. The rearrangement of β -glyceryl esters to α -glyceryl esters has been fairly extensively studied.¹¹ The acid-catalyzed rearrangement is considered to be an equilibration^{11e,f} proceeding via a cyclic acetal intermediate. The preparation by independent synthesis¹² of certain analogous acetals has tended to support the mechanism proposed. However, the related rearrangements of propyl carbamates containing substituents on the carbon atom adjacent to the one bearing the carbamate function have not previously been reported.

We found that the treatment of either Ie or If with thionyl chloride in pyridine led to one and the same chlorocarbamate¹³ for which we are suggesting the structure VIII on the basis of the fact that it reacts



with nitrous acid¹⁴ to yield Marle's chlorohydrin IV, identified by its refractive index and by the melting point of its phenylurethane. Further, IV, on treatment with phosgene followed by ammonia, yields VIII. Since a rearrangement must have occurred during the reaction of Ie with thionyl chloride,¹⁵ the validity of a degradative method for establishing the structure of α -hydroxycarbamates whose first step involves replacement of -OH by -Cl is open to serious question.^{16,17}

(11) (a) E. Fischer, Ber., 53, 1621 (1920); (b) H. Hibbert and N. M. Carter, J. Am. Chem. Soc., 51, 1601 (1929) and earlier literature cited therein; (c) B. F. Stimmel and C. G. King, J. Am. Chem. Soc., 56, 1724 (1934); (d) B. F. Daubert and C. G. King, J. Am. Chem. Soc., 50, 3003 (1938); (e) J. B. Martin, J. Am. Chem. Soc., 75, 5483 (1953); (f) P. E. Verkade and O. E. Van Lohuizen, Koninkl. Med. Akad. Wetenschap., Proc., Ser. B., 56, 324 (1953), Chem. Abstr., 49, 1557i (1955); (g) F. Aylward and P. D. S. Wood, Chemistry and Industry, 53 (1956).

(12) H. Hibbert and M. E. Greig, Can. J. Research, 4, 254 (1931); Chem. Abstr., 25, 2973i (1931).

(13) Identity verified by infrared spectra.

(14) It is taken for granted that in the nitrous acid reaction there is no disturbance of the bonds between C-1 and C-2 and their respective substituents so that further rearrangement during this deamination-decarboxylation is impossible.

(15) In a somewhat analogous situation which illustrates the migratory possibility of the chlorine atom, Suzuki and Inoue, *Proc. Imp. Acad.* (*Tokyo*), **6**, 71 (1930), *Chem. Abstr.*, 24, 4265 (1930) had found that both 1-chloro-2,3-dihydroxypropane and 2-chloro-1,3-dihydroxypropane give the same di-*p*-nitrobenzoyl derivative, namely 1,3-bis-*p*-nitrobenzoyl-2-chloropropane.

(16) H. Najer, P. Chabrier, and R. Giudicelli, Bull. soc. chim. France, 1142 (1954).

(17) M. M. Baizer, J. R. Clark and E. Smith, J. Org. Chem., 22, 1706 (1957).

⁽⁹⁾ Experiments by D. Regenbogen, T. Swindlehurst, Jr., and K. K. Haber.

⁽¹⁰⁾ E. R. Marle, J. Chem. Soc., 316 (1912).

A second shift occurs, at least in part, when VIII is treated with freshly prepared silver oxide in 50% isopropyl alcohol: a small yield of Ie was then the only definite product isolated from this reaction.¹⁸ These rearrangements may be rationalized as indicated.



The acyclic carbonium ions IX-X which may be written to represent formally the initial products of reaction form a common cyclic transition cation, the aggregate of whose resonance forms can be represented by XI. When the environment contains Cl^- , attack appears to proceed predominantly at C-1; when OH^- is present, attack occurs at least in part at C-2.

In an effort to increase the overall yield of Ie from IIa attempts were made to rearrange If to Ie. When If (m.p. 117-119°) was heated under reflux in toluene containing a catalytic amount of p-toluenesulfonic acid, the melting point was lowered (94-112°) but upon recrystallization of the crude product only If could be recovered. When allowed to stand overnight at room temperature in chloroform saturated with hydrogen chloride, If was converted almost completely to its dioxolone; under the same conditions Ie yielded about 45% of the dioxolone and 42% of unchanged starting material. Neither If nor Ie reacted at room temperature with two moles of hydrogen chloride in isopropyl alcohol, but at 50-60° they were converted to the dioxolone in 33% and 40% yield respectively.¹⁹ Obviously the carbamates were stable to small amounts of acid and in the presence of larger quantities lost ammonia and underwent recyclization.

The rearrangement of If with the aid of strong alkaline catalysts capable of supplying alkoxide or hydroxide ions, however, was successful. Stirring a suspension of If in isopropyl or ethyl alcohol overnight at room temperature with about two mole percent of catalyst in the presence of an ammonia atmosphere yielded about 60-65% of pure Ie.²⁰ Sodium ethoxide, sodium isopropoxide, sodium hydroxide, and benzyltrimethyl ammonium hydroxide were effective catalysts; piperidine was inoperative. After the rearrangement and removal of the pure Ie formed, the second crop material could again be rearranged to Ie in the same yield as above.

The virtual identity of the yield of Ie in a given period from either IIa or from If (or from Ie second crops), the observed liberation of ammonia during the rearrangement conducted in the absence of added gas, and the equilibration of Ie under similar conditions to a mixture from which 60-65% of Ie can be recovered strongly suggest that the rearrangement described here occurs via ring closure of the carbamates to IIa followed by ring-opening to give Ie and If in an approximately 7:3 ratio.

EXPERIMENTAL²¹

1-Carbamoxy-2-hydroxy-3-(o-methoxyphenoxy)propane (Ie). To 396.4 g. (2.0 mole) of molten (100°) 1,2-dihydroxy-3-(o-methoxyphenoxy)propane was added with stirring 5.6 g. (0.1 mole) of sodium methylate and 472 g. (4.0 mole) of diethyl carbonate. The mixture was heated with stirring, and the ethanol which formed distilled at 79-84°. When the internal temperature was 130°, heating was stopped, and 6 g. of ammonium chloride was added. The remainder of the ethanol and excess diethyl carbonate were then distilled *in vacuo* (25 mm.) to an internal temperature of 130°. The residue, crude dioxolone, IIa, was used without purification for the next step. A small amount of the residue was recrystallized from ethyl acetate; m.p. $68.4-69.0^{\circ}$.

Anal.²² Calcd. for C₁₁H₁₂O₅: C, 58.92; H, 5.40. Found: C, 59.04; H, 5.30.

The still warm (50°) crude molten IIa was mixed with 100 ml. isopropyl alcohol and added with stirring to a solution of 68 g. (4 mole) of ammonia in 2400 ml. of the alcohol. The mixture was stirred overnight at room temperature in a tightly stoppered flask. At first a dense almost unstirrable precipitate formed which dissolved and then reprecipitated. The 2-propanol and ammonia were removed in vacuo (120 mm.) on a steam bath. The residue was dissolved in 2400 ml. of hot ethyl acetate, treated with charcoal, and filtered. On cooling, 304 g. (63.4%) of Ie, m.p. 95-96.5° was obtained. No depression was observed in a mixture melting point with Ie prepared by Murphey's⁴ procedure from 1,2dihydroxy-3-(o-methoxyphenoxy)propane, phosgene, and ammonia. A second crop, 142 g. (28.4%), m.p. 90-105° was obtained. This substance was rearranged (see separate section on rearrangement) to yield 94 g. (19.5%) more of Ie, m.p. 94.5-96.0°. Another 8.4 g. (1.7%) was obtained by rearranging 15.4 g. (3.2%) of a third crop obtained from the mother liquors of the rearranged second crop; m.p. 94.5-96.0°. The total of Ie was 406.4 g. (84.6%).

Isolation of 1-hydroxy-2-carbamoxy-3-(o-methoxyphenoxy)propane (I,). A kilogram of partly solvent-free (400 g. solid) mother liquor from several Ie preparations was recrystallized from 2 liters of ethyl acetate. The mother liquor was

⁽¹⁸⁾ The reaction is complicated by the possibility that simultaneous dehydrohalogenation occurs.

⁽¹⁹⁾ There was continuous evolution of carbon dioxide, indicating further decomposition of the dioxolone.

⁽²⁰⁾ The rearrangement also occurred when the mixture was heated under reflux for 24 hours, but in this case ammonia escaped and, although the yield of Ie was normal, no useful product could be obtained from the mother liquor.

⁽²¹⁾ Melting points are corrected, boiling points are not. (22) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, L. I., N. Y.

concentrated to 1200 ml. and chilled to give 113 g. of impure If, m.p. 116-118° which gave 85 g. m.p. 117-119° upon recrystallization from ethyl acetate.

Anal. Calcd. for $C_{11}H_{15}O_6N$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.96; H, 6.12; N, 5.98.

1-Carbamoxy-2-hydroxy-3-(o-methylphenoxy)propane (Mephenesin carbamate). In analogous manner 91 g. (0.5 mole) of 1,2-dihydroxy-3-(o-methylphenoxy)propane (Mephenesin), 1.4 g. of sodium methylate, 118 g. (1 mole) of diethyl carbonate were allowed to react. The crude dioxolone (II, $R = CH_3$) was again used without further purification. A sample of the dioxolone recrystallized from methanol melted at 95.4-96.0°.23 To the crude dioxolone suspended in 300 ml. of dry toluene at 45° was added with stirring a solution of 17 g. (1 mole) of ammonia in 200 ml. of anhydrous 3 A alcohol. The mixture was stirred overnight at room temperature. The alcohol and ammonia were removed by distillation. The hot toluene solution was charcoaled and chilled to yield 101 g. (89.7%) of crude Mephenesin carbam-ates, m.p. 72-81°. For separation of 1-carbamoxy-2-hydroxy-3-(o-methylphenoxy)propane, the crude product was recrystallized from 505 ml. of 50% aqueous acetic acid to give 56.7 g. of a hydrate, m.p. 82-84°. Upon recrystallization from benzene with initial removal of water by azeotropic distillation, 54.8 g. (48.0%) of Mephenesin carbamate, m.p. 92-93.5° was obtained.24

Rearrangement of If to Ie. (a) To a mixture of 12.1 g. (0.05 mole) of If and 80 ml. of a saturated solution of ammonia in ethanol was added a solution of 0.056 g. (0.0025 g.-atom) of sodium in 20 ml. of anhydrous 3 A alcohol. The mixture was stirred overnight at room temperature in a tightly stoppered flask. The solid soon dissolved to form a cloudy solution. Ammonium chloride (0.2 g.) was added, the ethanol was removed, the residue dissolved in 50 ml. of hot 2-propanol, charcoaled, and chilled to give 7.7 g. (63.6%) of Ie, m.p. 94-96°; no depression in mixed mething point with Ie previously obtained. Similar results were obtained with isopropyl alcohol as a solvent, and with sodium hydroxide, and benzyltrimethylammonium hydroxide as the bases. No rearrangement occurred with piperidine or Dowex 1-X (hydroxide cycle).

(b) A mixture of 142 g. (0.59 mole) of second crop obtained in the initial Ie preparation described above, m.p. $90-105^{\circ}$, and a solution of 15 g. (0.88 mole) of ammonia and 0.56 g. (0.024 mole) of sodium in 1200 ml. of 2-propanol was stirred overnight at room temperature in a tightly stoppered flask. Ammonium chloride (0.8 g.) was added, and the 2-propanol and ammonia removed in vacuum (120 mm.) on a steam bath. The residue was dissolved in 700 ml. of hot ethyl acetate, charcoaled, and chilled to give 94 g. (66.1%) of Ie, m.p. 94.5-96.0°. From the mother liquor by concentration was obtained 15.4 g. of a third crop m.p. 114-116° which upon treatment with 1.8 g. of ammonia and 0.08 g. of sodium dissolved in 120 ml. of 2-propanol gave 8.4 g. (54.6%) of Ie, m.p. 94.5-96.0°.

Reaction of Ie and If with hydrogen chloride. (a) In chloroform. A mixture of 4.82 g. (0.02 mole) of Ie and 50 ml. of a saturated hydrogen chloride solution in chloroform was allowed to stand overnight at room temperature. After removal of chloroform and hydrogen chloride, the residue was recrystallized from benzene to give 2.0 g. (40%) of Ie, m.p. 92–94°. Evaporation of the mother liquor and recrystallization of the residue from 2-propanol yielded 2.0 g. (44%) of IIa, m.p. 66–67°; no depression in mixed melting point with previously obtained material. If gave mostly IIa; only a few crystals m.p. 108–112° were also isolated.

(b) In 2-propanol. A solution of 1.8 g. (0.044 mole) of hydrogen chloride in 32 ml. of 2-propanol and 4.82 g. (0.02 mole) of Ie was heated overnight at 55-60°. Ammonium chloride (0.91 g., 88.5%) was removed by filtration of the hot solution. Upon chilling, 1.5 g. (33.4%) IIa, m.p. (after

recrystallization from 2-propanol) 68–70°, no depression in mixed melting point with previously obtained material. If gave 1.8 g. (40%) of IIa in a similar reaction.

1,2-Epoxy-3-benzyloxypropane (III). To 12.5 g. of fine sodium shot in 300 ml. of dry toluene was added 50.4 g. (0.5 mole) of benzyl alcohol. After stirring overnight at room temperature, the preparation of sodium benzylate was completed by refluxing until no more sodium remained. A thick suspension resulted to which 49.5 g. (0.52 mole) of epichlorohydrin was added after cooling to room temperature. The mixture was heated to 80° at which point a vigorous reaction started. The reaction subsided in 5-10 min., and reflux was continued for 1.5 hr. more. The mixture was cooled, water and dilute hydrochloric acid were added to neutrality, and the toluene layer separated. The aqueous was extracted with toluene. After drying (sodium sulfate) the toluene solution and distilling 14.7 g. (17.9%) of III, b.p. 76-81°/0.3-0.7 mm., n_D^{25} 1.5148-1.5150 was obtained.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.22; H, 7.37. Found: C, 73.25; H, 7.27.

1-Benzyloxy-2-hydroxy-3-(o-methoxyphenoxy)-propane (V). (a) To 2.48 g. (0.02 mole) of guaiacol in 10 ml. of toluene, in which 0.05 g. of sodium was dissolved, was added 1.64 g. (0.01 mole) of III in 10 ml. of toluene. After 7 hr. of reflux, the reaction mixture (cold) was extracted with 1N sodium hydroxide to remove excess guaiacol. The toluene solution gave upon distillation in high vacuum (Hickman still) 1.06 g. (36.8%) of V, n_D^{25} 1.5577; b.p. 120-130°/0.0005 mm. (bath temperature).

(b) To a solution of 0.67 g. (0.03 g. atom) of sodium in 25 ml. of dry benzyl alcohol was added 6.52 g. (0.03 mole) of 1-chloro-2-hydroxy-3-(o-methoxyphenoxy) propane (IV).¹⁶ The mixture was heated to 110-120° for 24 hr., cooled, 100 ml. of ether added, and the salts filtered (1.92 g.; theory for sodium chloride, 1.76 g.). The ether solution was washed with water, dried (sodium sulfate) and distilled (Hickman still) to give 6.19 g. (71.5%) of V, b.p./0.5-5 μ 125-145° (bath temperature), n_{25}^{25} 1.5576-1.5594.

A sample was redistilled for analysis; b.p./1 μ 120° (bath temperature); n_D^{25} 1.5572.

Anal. Calcd. for C₁₇H₂₀O₄: C, 70.81; H, 6.99. Found: C, 72.31, 72.06; H, 7.14, 7.10.

This substance was somewhat impure. The products from both reactions gave the same *p*-nitrobenzoate with *p*-nitrobenzoyl chloride and pyridine; m.p. $73-75^{\circ}$; no depression in mixed melting point.

Anal. Caled. for C₂₄H₂₃O₇N: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.08; H, 5.09; N, 3.27.

1-Benzyloxy-2-carbamoxy-3-(o-methoxyphenoxy)propane (VI). To a solution of 1.18 g. (0.012 mole) of phosgene in 15 ml. of dry toluene was added with stirring at 0-5° in 1 hr. 2.88 g. (0.01 mole) of V and 1.70 g. (0.014 mole) of dimethylaniline in 10 ml. of dry toluene. The mixture was stirred for 2.5 hr. at 0-5°, 10 ml. of ice water added, and the toluene layer removed. It was washed with 10 ml. of cold (5°) 2% hydrochloric acid, 10 ml. of ice water, and stirred with 2.2 g. (0.04 mole) of concentrated aqueous ammonia for 2 hr. at 0-10° and for 1 hr. at 25°. The toluene solution was washed with water, dried (sodium sulfate), and the toluene removed. The residue was triturated with hexane to give 3.4 g. of crystals m.p. 50-64°. Upon two recrystallizations from diisopropyl ether, 1.75 g. (52.8%) of VI, m.p. 74.5-76.0° was obtained.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.20; H, 6.25; N, 4.33.

1-Hydroxy-2-carbamoxy-3-(o-methoxyphenoxy)propane (If). A solution of 0.29 g. (0.88 millimole) of VI in 18 ml. of 2propanol was hydrogenated over 0.15 g. of 15% Pd/C atroom temperature and atmospheric pressure. After 3 hr., 21.6 ml. (theory 19.7 ml.) of hydrogen was absorbed. The mixture was filtered and concentrated to a small volume. Upon cooling, 0.16 g. (76%) of crude If, m.p. 104-116° crystallized; m.p. 117-119° upon recrystallization from ethyl acetate. No depression in mixture melting point with

⁽²³⁾ Reported⁶ 96-97°.

⁽²⁴⁾ Reported⁶ 93-94°.

If isolated from Ie reaction mixtures was observed. The infrared absorption spectra of both were identical.²⁶

1-Chloro-2-carbamoxy-3-(o-methoxyphenoxy)propane (VIII). (a) From Ie. To a mixture of 120.6 g. (0.50 mole) of Ie, 47.5 g. (0.50 mole) of dry pyridine, and 500 ml. of dry benzene was added with stirring at 0-10° in 1 hr. 65.4 g. (0.55 mole) of thionyl chloride. The mixture was then slowly heated to reflux until the evolution of sulfur dioxide stopped (constant internal temperature) and for 30 min. more. Water (200 ml.) was added to the cooled (25°) reaction mixture. Two liquid phases which crystallized rapidly formed. After filtration and washing with water and benzene, 111.4 g. (87.6%) of VIII, m.p. 105-106° was obtained.

(b) From If. To an ice cooled solution of 2.41 g. (0.01 mole) of If in 1.10 g. (0.014 mole) of dry pyridine was added 1.5 g. (0.0125 mole) of thionyl chloride. After 1 hr. at room temperature and several minutes on the steam bath, water was added to the cooled reaction mixture. The crude product was filtered and recrystallized from 2-propanol to give 1.67 g. (64.5%) of VIII, m.p. $104-104.5^\circ$; m.p. $105.5-106.5^\circ$ after recrystallization (2-propanol).

(c) From IV. To a stirring solution 20 g. (0.0923 mole) of IV in 135 ml. of dry toluene at 20° was added 9.9 g. (0.10 mole) of phosgene in 100 ml. of dry toluene. After 1 hr. at room temperature, 12.1 g. (0.10 mole) of dimethylaniline in 75 ml. of toluene was added below 20°. The toluene solution was washed with ice water, ice cold 5% hydrochloric acid, ice water, and added, at 0-5°, to 170 ml. of concentrated aqueous ammonia. After 4 hr. at 0-5°, the

(25) A Perkin-Elmer Model 21 was used.

product, 4 g. (16.6%), was filtered and recrystallized twice from 2-propanol; m.p. 105–106.5°.

All three preparations showed no depressions in mixed melting points.

All gave the same infrared absorption spectra.

Anal. Calcd. for $C_{11}H_{15}O_4CIN$: Cl, 13.65; N, 5.39. Found: Cl, 13.58; N, 5.54.

Reaction of VIII with nitrous acid. To a solution of 6.8 g. (0.026 mole) of VIII in 50 ml. of acetic acid was added with stirring at 80°C in 30 min. 5 g. of sodium nitrite in 10 ml. of water. The mixture was poured into 250 ml. of water, and extracted with benzene. The benzene was removed, and the residue recrystallized from fresh benzene to give 2.2 g. (32.4%) of unchanged VIII, m.p. 104-106°C. The mother liquor was distilled (Hickman still) to give 1.7 g. (30.7%) of IV, b.p./1 μ 90-100° (bath temperature), n_D^{25} 1.5430. A phenyl urethane m.p. 118.5-119.5° was obtained with phenyl isocyanate; no mixed melting point depression with the urethane from IV obtained by Marle's¹⁰ method, m.p. 119.5-120.5°.

Reaction of VIII with silver hydroxide. A mixture of 5.6 g. (0.02 mole) of VIII and freshly precipitated silver hydroxide (from 3.4 g., 0.02 mole, of silver nitrate) in 60 ml. of 50%2-propanol was refluxed for 4 hr. After filtration, removal of solvent, and benzene recrystallization, 1.0 g. of crystals m.p. 78-88° was obtained. Upon recrystallization from 2propanol, 0.5 g. of Ie m.p. 94-96°C was obtained. No depression in mixed melting point with Ie previously prepared was observed.

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY AT HARVARD UNIVERSITY]

Cycloalkyl- and Secondary Alkyltin Compounds and Their Cleavage by Iodine in Benzene Solution

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The preparation of $(\text{cyclo-C}_{6}H_{9})_{2}\text{SnR}_{2}$ and $(\text{cyclo-C}_{6}H_{11})_{2}\text{SnR}_{2}$ ($\mathbf{R} = Me, n$ -Bu, $C_{6}H_{5}$), $(\text{sec.-Bu})_{2}\text{SnMe}_{2}$, $(\text{iso-Pr})_{2}\text{SnR}_{2}$ ($\mathbf{R} = Me, n$ -Bu), and n-Bu₂SnMe₂ is described. These compounds were cleaved by the action of one equivalent of iodine in refluxing benzene solution to give mixtures of both possible cleavage products, except in the case of those compounds which contained phenyl groups. In the latter compounds only phenyl cleavage was observed. Twelve new organotin iodides of formula R₂R'SnI are described.

Only two publications have thus far been concerned with cycloalkyltin compounds.^{2,3} Similarly, organotin compounds containing secondary alkyl groups have been the subject of only a small number of studies.⁴⁻⁶

Little is known of the position of cycloalkyl and secondary alkyl groups in the cleavage series for organotin compounds. It has been established that the phenyl group is cleaved in preference to the cyclohexyl group by the action of concentrated hydrochloric acid on $(cyclo-C_6H_{11})_2Sn(C_6H_5)_{2,3}$ thus showing that the latter group behaves like an aliphatic group. However, no experiments have been reported which determine the place of a cycloalkyl group in the aliphatic organotin cleavage series. It was stated by Luitjen and van der Kerk (ref. 6, p. 80) that secondary alkyl groups are cleaved from a tin atom prior to *n*-alkyl groups, but a quantitative product study of only one reaction⁴

 $(n-C_4H_9)_3SnC_4H_9$ -sec. + $I_2 \longrightarrow (n-C_4H_9)_3SnI + sec.-C_4H_9I$

appears to provide experimental proof for this generalization.

We now wish to report the preparation of a number of cyclopentyl-, cyclohexyl-, and secondary alkyltin compounds and the results of the cleavage of

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