Reactions of Amines. XV. Synthesis of α-Amino Acids from Imino Esters[1,2]

HENRY E. BAUMGARTEN, JERALD E. DIRKS, JAMES M. PETERSEN, AND ROBERT L. ZEY

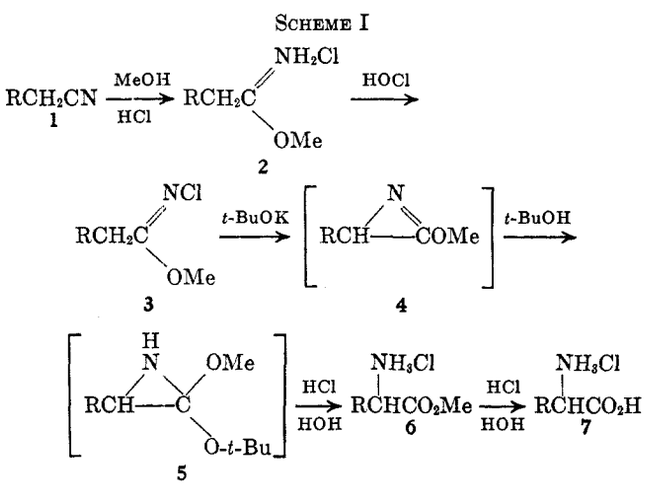
Avery Laboratory, University of Nebraska, Lincoln, Nebraska 68508

Received May 9, 1966

Substituted alkyl acetimidates **2** were halogenated on nitrogen with hypochlorous acid; the resulting N-chlorimino esters **3** were subjected to base-catalyzed rearrangement, possibly proceeding through the azirine **4** or aziridine **5** intermediates. Subsequent acid hydrolysis of the intermediates gave the α-amino acid esters **6** or, by more vigorous hydrolysis, the α-amino acids **7**.

In an earlier communication an apparently general synthesis of α-amino ketones by a Neber-like rearrangement of N-chloroketimines was described.[3] The purpose of the present investigation was to determine whether or not one of the alkyl groups of the N-chloroketimine could be replaced by an alkoxy group, giving thereby a Neber-like rearrangement of an N-chloroimino ester to an α-amino acid ester. The reaction scheme is illustrated in the sequence **1** → **7** (Scheme I). The exactly analogous Neber rearrangement has not been reported.

SCHEME I



Insofar as we have been able to determine, the only reported syntheses of N-haloimino esters are those of Steiglitz[4] and of Houben and Schmidt.[5] Steiglitz[4] prepared ethyl N-chlorobenzimidate by addition of solid ethyl benzimidate hydrochloride (prepared by the Pinner synthesis) to cold, aqueous sodium hypochlorite solution. Using the same general procedure Houben and Schmidt[5] prepared ethyl N-chloro-, N-bromo-, and N-iodoacetimidate. The compounds prepared were well characterized but their reactions were not studied extensively.

In our experiments the nitriles **1** were converted into the methyl or ethyl imino ester hydrochlorides **2** by McElvain's procedure for the Pinner synthesis.[6] The N-chloroimino esters **3** could be prepared by treatment of the free imino esters (obtained by neutralization of **2** with potassium carbonate[7]) with *t*-butyl hypochlorite as in the preparation of N-chloroketimines;[3] however, the manipulations were more involved and yields of **3** were lower than those obtained using the original Steiglitz procedure, which was, therefore, the procedure of choice. Generally, **3** was not isolated but was immediately subjected to base-catalyzed rearrangement. However, to demonstrate that isolation was feasible, two of the lower homologs of **3** were isolated, purified by distillation under reduced pressure, and analyzed without undue difficulty.

The base-catalyzed rearrangement of **3** was much more sensitive to reaction conditions than the rearrangement of N-chloroketimines. For example, when *hot* methanolic sodium methoxide was used in the rearrangement of methyl N-chlorophenylacetimidate (**3**, R = C_6H_5), only a 14% yield of α-aminophenylacetic acid resulted. Under similar conditions in the rearrangement of methyl N-chlorohydrocinnamimidate (**3**, R = $C_6H_5CH_2$) none of the expected phenylalanine was obtained. However, when *cold* ethanolic sodium ethoxide was used, the yields of the two amino acids were 75 and 20%, respectively. These and other experiments indicated that conditions suitable for the rearrangement of N-chloroketimines were either unsatisfactory or less satisfactory for the rearrangement of N-chlorimino esters.[8] The principal factors responsible for these differences appeared to be the much lower reactivity of the α hydrogens of the N-chlorimino esters relative to those of the N-chloro ketimines and the greater lability of the intermediates (presumably **4** or **5**) toward decomposition by heat and/or excess base. Thus, for all but the most reactive N-haloimino esters the optimum reaction conditions for rearrangements involved use of the strong base, potassium *t*-butoxide, at temperatures near 0°. Under these conditions, for example, the yield of phenylalanine was 60%.

Either the α-amino acid **7** or its alkyl ester **6** could be isolated as product, depending upon the vigor of the acid cleavage of the presumed intermediate, **4** or **5**. As expected, acid cleavage always gave the ester corresponding to the alcohol used in the sequence **1** → **2** rather than the *t*-butyl ester.

The results of a number of experiments using this procedure are tabulated in Table I.

Unfortunately, as in most α-amino acid syntheses, the supposedly optimum procedure failed to yield α-amino acids from a number of nitriles. In only one of

(1) Paper XIV: H. E. Baumgarten and A. Staklis, *J. Am. Chem. Soc.*, **87**, 1141 (1965).

(2) This work was supported in part by grants G-11339 and G-21405 of the National Science Foundation. A preliminary report of parts of this work appeared in H. E. Baumgarten, J. E. Dirks, J. M. Petersen, and D. C. Wolf, *J. Am. Chem. Soc.*, **82**, 4422 (1960).

(3) H. E. Baumgarten, I. M. Petersen, and D. C. Wolf, *J. Org. Chem.*, **28**, 2369 (1963).

(4) J. Steiglitz, *Am. Chem. J.*, **18**, 751 (1896).

(5) J. Houben and E. Schmidt, *Ber.*, **46**, 3616 (1913).

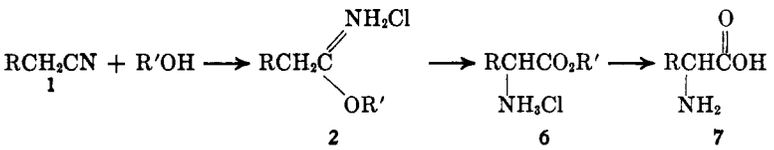
(6) S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64**, 1825 (1942); S. M. McElvain and C. L. Stevens, *ibid.*, **68**, 1914 (1946).

(7) S. A. Glickman and A. C. Cope, *ibid.*, **67**, 1017 (1945).

(8) In retrospect it might appear that the rearrangement of N,N-dichloroamines and N-chlorimines[3] should also be carried out under the conditions employed for N-chlorimino esters, but this speculation has not been verified experimentally. In the few experiments tried N,N-dichloramines and N-chlorimines gave better results with *hot* sodium alkoxide solutions.

TABLE I

SYNTHESIS OF α-AMINO ACIDS



R	R'	Yield of 2, %[a]	Base	Yield of 6, %[b]	Mp of 6, °C	Yield of 7, %[b,c]
H	CH_3	92	*t*-BuOK	51	175[d]	47–51
CH_3	CH_3	75–94	*t*-BuOK	40–58	157[e]	55
	CH_3CH_2	65–72	*t*-BuOK	*f*		50[g]
			EtONa	0		0
$CH_3(CH_2)_2$	CH_3	44–54	*t*-BuOK	59	114–115[h]	48
	CH_3CH_2	68–70	*t*-BuOK	*f*		22–23[i]
$(CH_3)_2CHCH_2$	CH_3	90	*t*-BuOK	65	110–113[j]	58–66
	CH_3CH_2	62	*t*-BuOK	*f*		20–22
Cyclohexyl	CH_3	62–73	*t*-BuOK	*f*		0
$C_6H_5CH_2$	CH_3CH_2		EtONa	*f*		21–32[k]
			t-BuOK	*f*		60[k]
$NC(CH_2)_3$	CH_3CH_2	92	*t*-BuOK	*f*		Low[l]
C_6H_5	CH_3	75–78	MeONa	69–75	222[m]	64–71
	CH_3CH_2	71–100	EtONa	52	201[n]	54–75
p-$CH_3C_6H_4$	CH_3	74	MeONa	*f*		67[o]
p-ClC_6H_4	CH_3	80	MeONa	*f*		55[p]
p-$CH_3OC_6H_4$	CH_3	64–77	MeONa	18–20	187–189[q]	17–19[n]
	CH_3		*t*-BuOK	32		31[r]
p-$NO_2C_6H_4$	CH_3	25	MeONa	*f*		0
			t-BuOK	*f*		0
α-Naphthyl	CH_3	79–89	MeONa	44–54	177–178.5[s]	43–52[t]

[a] Yield of crude, dry product. [b] Based on **2**. Many of these compounds were very hygroscopic. [c] Unless otherwise indicated amino acids were identified by comparison of infrared spectra (KBr) with those of authentic samples. [d] H. Werbin and P. E. Spoerri [*J. Am. Chem. Soc.*, **69**, 1681 (1947)] report mp 175–176°. [e] A. L. Barker and G. S. Skinner [*ibid.*, **46**, 403 (1924)] report mp 158–158.5°. [f] Not isolated. [g] Yield from N-chloroimino ester, 78%. [h] E. L. Smith and W. G. Polglase [*J. Biol. Chem.*, **180**, 1209 (1949)] report mp 115–116°. [i] Yield from N-chlorimino ester [80% yield, bp 47° (2 mm), active Cl, 98.2%], 27–29%. [j] K. Weil and W. Kuhn [*Helv. Chim. Acta*, **29**, 784 (1946)] report mp 113–114°. [k] Yields based on free imino ester (see Experimental Section). Yield based on nitrile was 79% of these values. [l] Appeared to be a mixture of stereoisomeric amino acids. [m] A. Kossel [*Ber.*, **24**, 4145 (1891) reports mp 224°. [n] A. Darapsky [*J. Prakt. Chem.*, **207**, 179 (1919)] reports mp 202° dec. [o] Sublimed at 225–227°; A. Darapsky, J. Loevenich, O. Creifelds, W. Bellinger, E. Koster, V. Binet, H. Wasserfuhr, and H. Beck [*J. Prakt. Chem.*, **146**, 268 (1936)] report sublimation at 220°. [p] Sublimed at 230°; E. K. Harvill and R. M. Herbst [*J. Org. Chem.*, **9**, 21 (1944)] report mp 261–262°, sublimed below melting point. [q] *Anal.* Calcd for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.04. Found: C, 51.52; H, 6.39; N, 5.79. [r] Sublimed at 229–230° (footnote *p*, mp 284–285° dec, sublimed at 230°). [s] *Anal.* Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.57. Found: C, 61.79; H, 5.75; N, 5.70. [t] *Anal.* Calcd for $C_{12}H_{10}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.11; H, 5.62; N, 7.05.

several experiments did cyclohexyl cyanide give even a trace of an α-amino acid ester. In these experiments the disappearance of active halogen required a relatively long period of time; thus, the failure of the method may be attributed to the low reactivity of the hydrogen α to the imino ester function.[9] Monocyanoethylated morpholine and dicyanoethylated methyl ethyl ketone gave very low yields of the corresponding imino ester hydrochloride. *p*-Nitrophenylacetonitrile gave the known imino ester but none of the corresponding amino acid. Very probably these failures were due to an unfortunate choice of reaction variables. If so, they call attention to the small margin of difference between success and failure in this reaction. Of the several reactions of N-halo compounds studied in this laboratory, the reaction described herein has been the most demanding on experimental technique and choice of reaction conditions. However, once the experimental operations are mastered the sequence is capable of giving good yields of many α-amino acids.

(9) Under such conditions the principal mode of attack by *t*-butoxide ion is probably on chlorine rather than on hydrogen, the chlorine being removed as *t*-butyl hypochlorite. This appears to be an important side reaction of N-haloamines and N-haloamides with strong bases, as will be delineated more specifically in later papers in this series.

Several attempts were made to isolate intermediates such as **4** and **5** (which is of especial interest, being a ketal of an α-lactam). These were not successful; however, in view of the inherent interest in these unusual structures and the recent successful isolation of similar substances, the further exploration of such isolation appears desirable.

Experimental Section[10]

Preparation of Imino Ester Hydrochlorides.—The imino ester hydrochlorides used in this study were prepared from the corresponding nitriles according to the procedures outlined by McElvain[6] for ethyl imino ester hydrochlorides. Oven-dried glassware was used for each preparation, and each nitrile was dried immediately before use by distillation from phosphorus pentoxide. Commercial absolute methanol was further dried by heating under reflux over magnesium turnings (1 g/100 ml of methanol) for a minimum of 4 hr. Commercial absolute ethanol was further dried by heating under reflux over magnesium ethoxide according to the procedure of Lund and Bjerrum.[11] Anhydrous hydrogen chloride was used directly from the tank without additional drying. The crude products of these preparations were used in this study without further purification.

(10) Analyses were by Micro-Tech Laboratories, Skokie, Ill. Melting points were corrected.

(11) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).

The procedure which was used for the preparation of methyl phenyl acetimidate hydrochloride and of ethyl hydrocinnamimidate are described in detail. Crude yields of the other imino esters are given in Table I.

Methyl Phenylacetimidate Hydrochloride.—A solution of 103.8 g (0.887 mole) of phenylacetonitrile and 28.4 g (0.887 mole) of absolute methanol was cooled in an ice–salt bath and treated with gaseous hydrogen chloride (at a rate which permitted the temperature to remain below 5°) until 34.9 g (0.942 mole) had been absorbed. The reaction mixture (protected from atmospheric moisture with a calcium chloride tube) was allowed to stand overnight in the refrigerator. To the resulting viscous liquid was added an equal volume of anhydrous ether and the mixture was stirred until a white solid formed. This mixture was cooled in Dry Ice for 2 hr and the solid was collected and washed with a small amount of cold anhydrous ether. The solid was dried overnight in a vacuum desiccator over sodium hydroxide pellets and phosphorus pentoxide. The yield of crude ethyl phenylacetimidate hydrochloride was 124 g (75%). This product was used without purification for the next step in the synthesis.

Other preparations of this imino ester hydrochloride, using the procedure outlined above, resulted in yields of 75–78% of the crude product. Yields of the ethyl ester varied from 71–100%. In one preparation of the latter using freshly opened phenylacetonitrile instead of the nitrile distilled from phosphorus pentoxide only 49.5% of the crude product was obtained.

Ethyl Hydrocinnamimidate.—The preparation of ethyl hydrocinnamimidate was carried out in the same manner as for the preparation of methyl phenylacetimidate. A solution of 30.9 g (0.235 mole) of hydrocinnamonitrile and 11.5 g (14.6 ml, 0.25 mole) of absolute ethanol was treated at −2° with anhydrous hydrogen chloride until 8.9 g (0.25 mole) of gas had been absorbed. After the mixture had stood in the refrigerator overnight the solid mass of crystals was collected and washed with dry ether, giving 41 g (82%) of crude ethyl hydrocinnamimidate hydrochloride. The hydrochloride salt was converted into the free base by the method of Glickman and Cope,[7] giving 31 g (79%) of ethyl hydrocinnamimidate, bp 129.5–130° (12 mm).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.11; H, 8.68; N, 7.63.

Preparation of α-Amino Acids.—In each of the following experiments an attempt was made to keep the rearrangement step as nearly anhydrous as possible. In addition to protecting each solution and the reaction mixture from atmospheric moisture with calcium chloride tubes, all glassware was oven dried at *ca.* 100° overnight. If ethanol or methanol was used, it was dried in the manner described previously. Anhydrous *t*-butyl alcohol was prepared by adding sodium to commercial *t*-butyl alcohol (3 g/100 ml of alcohol), heating under reflux until most of the sodium had reacted, and then collecting the dried alcohol by distillation. The metallic sodium or potassium was cut and weighed under a dry inert solvent. When *n*-pentane was used, the commercial product was dried by storing over sodium wire.

Ethyl N-Chlorophenylacetimidate (3, R = C_6H_5).—The preparation of ethyl N-chlorophenylacetimidate was carried out using the procedure of Steiglitz[4] as a model A solution of 100 g (2.5 moles) of sodium hydroxide in 800 ml of water was cooled in an ice-salt bath and 114.4 g (1.61 moles) of chlorine was added gradually while keeping the temperature below 5°. To the resulting cooled and stirred sodium hypochlorite solution was added gradually 29.5 g (0.15 mole) of crude ethyl phenylacetimidate hydrochloride. The resulting mixture was stirred for 30 min after the addition of the salt was complete and was extracted once with a 100-ml portion and twice with 50-ml portions of *n*-pentane. The combined pentane extracts were dried ($MgSO_4$) for 1 hr, filtered, and evaporated to a nearly colorless soil under the vacuum of a water aspirator. The yield of crude ethyl N-chlorophenylacetimidate was 29.38 g (99.2%).

The method of Steiglitz[4] was used to determine the amount of active chlorine present in the crude N-chloro compound.

Anal. Calcd for $C_{10}H_{12}ClNO$: active Cl, 17.93. Found: 16.24, 16.57. The results of these determinations indicated that the crude material contained approximately 90% of the desired chloro compound.[12]

α-Aminophenylacetic Acid (7, R = C_6H_5).—A solution of 14.7 g of crude ethyl N-chlorophenylacetimidate (prepared from 0.075 mole of the imino ester hyrochloride) in 75 ml of dry *n*-pentane, was added dropwise to a stirred and cooled sodium ethoxide solution prepared from 2.3 g (0.10 g-atom) of sodium and 75 ml of absolute ethanol. During this addition a white precipitate formed, and the mixture gradually changed in color from colorless to light tan. After the addition of the chloro compound was complete, the reaction mixture was stirred for an additional 20 min until 1 drop of it caused no color change of starch–iodide paper moistened with 1 *N* hydrochloric acid. The reaction mixture was poured into 100 ml of well-stirred 2 *N* hydrochloric acid. The organic layer was separated and washed twice with 20-ml portions of 2 *N* hydrochloric acid. The combined aqueous layers were heated under reflux for 1 hr, then evaporated to dryness under vacuum. The solid residue was extracted with 110 ml of cold water, and the resulting solution was neutralized with ammonium hydroxide. The precipitate which formed was collected by filtration, washed with cold water, and dried. The combined filtrates were acidified with hydrochloric acid and evaporated to dryness. The residue was extracted with 25 ml of cold water and the resulting solution was neutralized with ammonium hydroxide to give an additional crop of the product. The total yield of α-aminophenylacetic acid was 9.1 g (81%), based on the imino ester hydrochloride).

Purification of the crude amino acid was carried out according to the procedure of Steiger,[13] which gave 3.52 g (75%) of nearly white, lustrous platelets having no definite melting point.

In one experiment using the method outlined above, the reaction mixture turned very dark brown when the N-chloro compound was added to sodium ethoxide solution. In this case, only 20% of the amino acid was isolated from the aqueous layer obtained by pouring the rearrangement mixture into a hydrochloric acid solution. A large amount of dark red oil, which was not identified, remained in the organic layer. This observation was typical of those made in the course of the preparations of a number of different amino acids which gave low yields plus a red oil. The reason for these random failures was not determined.

In another preparation of α-aminophenylacetic acid by this method, only 23% of the amino acid was obtained on neutralization of the boiled aqueous extract. However, after standing for about 1 month at room temperature, the filtrate yielded an additional crop of 31% of the amino acid. This additional crop was produced by the gradual hydrolysis of the ester of the amino acid which had not been hydrolyzed by the boiling hydrochloric acid solution.

Ethyl α-Aminophenylacetate Hydrochloride (6, R = C_6H_5).—The crude ethyl N-chlorophenylacetamidate prepared as in the foregoing procedure from 9.98 g (0.050 mole) of the imino ester hydrochloride was added to a sodium ethoxide solution prepared from 1.40 g (0.061 g-atom) of sodium and 40 ml of anhydrous ethanol. As soon as the reaction mixture gave a negative starch–iodide test, it was poured into a well-stirred mixture of 24 ml of 4 *N* hydrochloric acid and 25 g of ice. The resulting layers were separated, and the organic layer was washed twice with 20-ml portions of 2 *N* hydrochloric acid. The combined aqueous extracts were evaporated to dryness under vacuum at temperatures below 45°. The resulting solid was extracted once with a 25-ml portion and twice with 5-ml portions of boiling ethanol, charcoal was added to these extracts, and the resulting mixture was cooled to room temperature and filtered. The filtrate was stirred vigorously and treated with 100 ml of anhydrous ether. The resulting mixture, after standing for 1 hr, was filtered to yield 3.9 g of the product. Evaporation of the filtrate to a volume of 10 ml, followed by cooling, filtering, and treating with 50 ml of ether, gave an additional 1.8 g of the product. The total yield of ethyl α-aminophenylacetate hydrochloride was 5.7 g, (52%), dec pt 201°.[14]

β-Phenylalanine (6, R = $C_6H_5CH_2$) (Using Sodium Ethoxide).—To a solution of 8.85 g (0.85 g (0.050 mole) of ethyl hydrocinnamimidate and 30 ml of dry *n*-pentane, cooled in an ice bath, was added 5.97 g (0.055 mole) of *t*-butyl hypochlorite diluted with 30 ml of dry pentane at such a rate that the temperature was maintained below 10°. After the addition was complete, the mixture was allowed to stand at room temperature for an additional 1 hr.

To a stirred solution of 1.38 g (0.060 g-atom) of sodium in 30 ml of ethanol, cooled in an ice–salt bath, was added dropwise

(12) A good qualitative estimate of the N-chlorimino ester content could be made by comparing the infrared band at 6.2 μ (N-chlorimino ester) with that at 5.7 μ (carboxylate ester).

(13) R. E. Steiger, Organic Syntheses, Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 84.

(14) See Table I, footnote *m*, dec pt 202°.

the solution of chlorinated imino ester. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature with periodic testing for active chlorine. After being stirred for 3 hr, the mixture still contained active chlorine. In spite of this fact, the reaction mixture was poured into 2 *N* hydrochloric acid and the aqueous layer was separated, refluxed for 5 hr, and evaporated to dryness. Isolation of the product in a manner similar to that used in the isolation of α-aminophenylacetic acid yielded 1.7 g (21%) of β-phenylalanine.

β-Phenylalanine (6, R = $C_6H_5CH_2$) (Using Potassium *t*-Butoxide).—To a stirred solution of potassium *t*-butoxide prepared from 4.6 g (0.12 g-atom) of potassium and 50 ml of anhydrous *t*-butyl alcohol was added dropwise a solution of ethyl N-chlorohydrocinnamimidate prepared as described in the preceding preparation from 9.80 g (0.0553 mole) of the imino ester and 6.00 g (0.0553 mole) of *t*-butyl hypochlorite. The reaction mixture was cooled in a cold-water bath. The resulting yellow mixture gave a negative starch–iodide test as soon as all of the chloro compound had been added. The hydrochloric acid extract of this mixture, after being heated under reflux and worked up as described in the previous experiment, yielded 5.5 g (60%) of β-phenylalanine.

Alanine (7, R = CH_3).—The following procedure is considered represent the optimum conditions developed thus far for the amino acids cited in Table I. A mixture of 150 ml of dry *t*-butyl alcohol and 5.80 g (0.148 mole) of metallic potassium was heated under reflux with stirring until all of the potassium had dissolved (about 3 hr), then cooled in an ice bath until the alcohol started to freeze.

While the foregoing solution was being heated, a solution of methyl N-chloropropionimidate was prepared. A solution of 20 g (0.50 mole) of sodium hydroxide in 200 ml of water was cooled in an ice–salt bath and treated with 16.7 g (0.23 mole) of chlorine gas at a rate such that the temperature remained below 10°. After the addition of the chlorine was completed, 5 ml of glacial acetic acid was added to the solution. To the resulting stirred and cooled solution 12.35 g (0.1000 mole) of methyl iminopropionimidate hydrochloride was added slowly through a powder funnel, the resulting mixture was stirred an additional 10 min, and then extracted once with a 50-ml portion and twice with 25-ml portions of *n*-pentane. The combined pentane extracts were dried ($MgSO_4$) in the refrigerator for at least 1 hr.

The dried pentane solution containing the methyl N-chloropropionimidate was filtered and added dropwise during a period of 25 min to the cooled potassium *t*-butoxide solution. As soon as the addition was completed, the ice bath was removed and the mixture was stirred at room temperature until 1 drop of mixture when placed on acidified starch–iodide paper, caused no color change. This required about 70 min. The reaction mixture was then poured into 100 ml of 2 *N* hydrochloric acid, the organic layer was separated and washed twice with 25-ml portions of 2 *N* hydrochloric acid, and the combined aqueous extracts were evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml of 2 *N* hydrochloric acid, and the solution was heated under reflux for 2 hr, then evaporated to dryness. This residue was extracted with one 50-ml portion and two 25-ml portions of boiling 95% ethanol. The combined alcoholic extracts were cooled to room temperature and filtered, 5 ml of water was added, and the resulting solution was treated with 6 ml of pyridine. The resulting mixture was cooled in the refrigerator for 1 day and filtered, and the resulting solid was washed with 25 ml of 95% ethanol and dried under vacuum giving 4.9 g (55%) of alanine.

In another experiment the procedure described above for ethyl N-chlorophenylacetimidate was followed, and a sample of ethyl N-chloropropionimidate was prepared from 21.23 g (0.05 mole of ethyl propionimidate hydrochloride. The *n*-pentane was evaporated, and the crude N-chloro compound was distilled under reduced pressure giving a 64.4% yield of a more nearly pure product, bp 60–61° (14 mm). The distillate showed no absorption in the 5.7-μ region of the infrared spectrum.[12] Analysis as described for ethyl N-chlorophenylacetimidate indicated an active chlorine content of 97.7%. Upon treatment of 6.98 g (0.050 mole) of this product with the potassium *t*-butoxide from 2.61 g (0.067 g-atom) of potassium and 50 ml of *t*-butyl alcohol as described above, 3.5 g (78%, based on the N-chloro compound) of alanine was isolated.

Preparation of Methyl α-Aminopropionate Hydrochloride (6, R = CH_3).—A *n*-pentane solution of methyl N-chloropropionimidate prepared from 12.35 g (0.100 mole) of methyl propionimidate hydrochloride was allowed to react with a solution of potassium *t*-butoxide as described in the foregoing procedure. As soon as the reaction mixture had given a negative starch–iodide test, it was poured into a mixture of 50 ml of 4 *N* hydrochloric acid and 50 g of ice. The aqueous layer was separated from the pentane layer and the former was evaporated to dryness under vacuum at a temperature below 45°. The resulting residue was extracted with boiling methanol and the filtrate was again evaporated to dryness. The residue was purified by dissolving it in the minimum amount of methanol and adding 100 ml of anhydrous ether with stirring. The resulting precipitate was collected and dried under reduced pressure giving 7.7 g of colorless powder. Evaporation of the filtrate to dryness and purification of the residue produced an additional 0.41 g of the product. The total yield of methyl α-aminopropionate hydrochloride was 8.1 g (58%), mp 157°.[15]

(15) See Table I, footnote *e*, mp 158°.

Synthesis of a D-Glucofuranosyl Nucleoside Derivative through an Oxazoline[1]

M. L. WOLFROM AND M. W. WINKLEY

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received June 6, 1966

A novel synthesis of crystalline 3′,5′,6′-tri-*O*-acetyl-2-methyl-α-D-glucofurano[2′,1′:4,5]-2-oxazoline (II) was effected by the action of chlorine on ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside. This 2-methyloxazoline derivative was utilized in acid-catalyzed fusion techniques to synthesize a phenolic glycoside and a nucleoside derivative of 2-amino-2-deoxy-D-glucofuranose.

Acyl migrations from oxygen to nitrogen[2] and from nitrogen to oxygen[3] have been established in the 2-amino-2-deoxy-D-glucose structure and for this an oxazoline derivative has been postulated as an intermediate.[4] Such intermediates have indeed been isolated as crystalline compounds for the 2-phenyl-2-oxazoline derivative in several cases[5–8] and utilized in glycoside synthesis.[6,7,9] Although a 2-methyloxazoline derivative of 2-amino-2-deoxy-D-glucose was once claimed,[4] it was later disproved.[10,11] We describe herein the crystalline 3′,5′,6′-

(1) Supported by Grants CA-03232(C6) and CA-03232-10 (The Ohio State University Research Foundation Project 759H-I) from the Department of Health, Education, and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md.

(2) T. White, *J. Chem. Soc.*, 1498 (1938).

(3) F. Micheel, F.-P. van de Kamp, and H. Wulff, *Ber.*, **88**, 2011 (1955).

(4) T. White, *J. Chem. Soc.*, 428 (1940).

(5) F. Micheel, F.-P. van de Kamp, and H. Petersen, *Ber.*, **90**, 521 (1957).

(6) H. Micheel and H. Köchling, *ibid.*, **90**, 1597 (1957); **93**, 2372 (1960).

(7) S. Konstas, I. Photaki, and L. Zervas, *ibid.*, **92**, 1288 (1959).

(8) R. Gigg and C. D. Warren, *J. Chem. Soc.*, 1351 (1965).

(9) F. Micheel and H. Köchling, *Ber.*, **91**, 673 (1958).

(10) F.-P. van de Kamp and F. Micheel, *ibid.*, **90**, 2054 (1957).

(11) D. H. Leaback and P. G. Walker, *Chem. Ind.* (London), 1012 (1957); D. H. Leaback and P. G. Walker, *J. Chem. Soc.*, 4754 (1957).