not controlled during the sodium borohydride reduction, the product is inactive probably because the lactone ring is hydrolyzed in the alkaline solution. It is possible that even at *p*H 8.2–8.5, some of the lactone is opened.

Partial Hydrolysis in Acid Solution.—No definite information could be obtained by heating Factor S in dilute acid. The partial decomposition of 4-oxopipecolic acid was probably the cause of these difficulties in the interpretation. For this reason partially reduced Factor S was used.

Dihydro S (15 mg.), obtained by reduction in the presence of platinum, was kept in concentrated hydrochloric acid at 37° for 3 days. The solution was evaporated in a desiccator over solid sodium hydroxide and phosphorus pentoxide. The hydrolysate was applied as a streak on a sheet of Whatman 3 MM paper, and developed (descending) with pyridine–acetic acid–water–butanol, 10:10:50:40.[39,40] The fluorescent bands near the solvent front (F_3, 0.94; F_2, 0.87; F_1, 0.79) were cut off. On the guide strip cut from the remaining paper were found one weakly fluorescent (F_0, 0.50) and five ninhydrin-positive bands (Na, 0.14; Nc, 0.18; Nd, 0.22; Ne, 0.27; Nf, 0.39; Ng, 0.58). To this paper was sewn a sheet of 3 MM paper of the same size as the surface removed. The chromatogram was developed again with the same solvent mixture, in order to improve the separation of the ninhydrin positive bands. All bands were cut out and eluted with 0.02 *N* acetic acid. The eluate was evaporated to dryness, dissolved in 0.5 ml. of 6 *N* hydrochloric acid and hydrolyzed at 100° during 24 hr. The hydrolysate was evaporated to dryness and examined by one- and two-dimensional paper chromatography. Color reactions (ferric chloride, *p*-nitrobenzoyl chloride–pyridine) were also used for the identification. Na and Nc were identified as the isomers of 4-hydroxypipecolic acid. There was always a weak band (Nb) at the upper edge of Na, but the amount was too small for identification. Nd and Ne gave Thr, AmBut, Pro. The amount of Nd was very small. If N-MePhe, which gives a much less sensitive ninhydrin reaction, had been present, it would not have been detected. Nf was PhGly and Ng N-MePhe; F_0 was 3 HyPicolinic acid, F_1 gave 3 HyPic, Thr, AmBut, Pro; and F_2 and F_3, 3 HyPic, Thr, AmBut, Pro, N-MePhe.

The same picture was obtained with partial hydrolysates (3, 4 and 5 days at 37° in concd. HCl) of Factor S, reduced with sodium borohydride, except that no 3-HyPic (F_0) was found. But another ninhydrin-positive band (Nh 0.69) was detected. This is thought to be partially reduced 3-hydroxypicolinic acid.

Partial Hydrolysis in Alkaline Solution.—Factor S (25 mg.), reduced with sodium borohydride, was dissolved in 0.5 ml. of 0.1 *N* sodium hydroxide and kept at 50° for 2 to 5 days. The solution was neutralized with 0.1 *N* hydrochloric acid, and the precipitate of starting material was centrifuged off. The supernatant was chromatographed on Whatman 3 MM paper, as described for the partial acid hydrolysis. Besides a broad fluorescent band (R_f 0.9) which gave all amino acids upon total hydrolysis, two ninhydrin-positive bands were detected. One (R_f 0.35) gave 4-HyPipec and PhGly, the other (R_f 0.7) N-MePhe and 4-HyPipec upon acid hydrolysis.

Edman Degradation.[90]—Hydro S (100 mg.) was treated with phenyl isothiocyanate at *p*H 8.9 after treatment with sodium hydroxide to open the lactone ring as described for Etamycin.[11] The same reaction was also performed, but without sodium hydroxide treatment, with hydrogenated Staphylomycin S acid. The acid peptide solution, after extraction of the phenylthiohydantoin, was evaporated at low temperature in a desiccator or by freeze-drying.

The progress of the degradation was determined by four methods: A, paper chromatography of the PTH's in pyridine–heptane, 3:7[91]; B, paper chromatography of the amino acids obtained by hydrolysis (24 hr.) of the PTH's in 6 *N* hydrochloric acid at 150°; C, or in hydroiodic acid (d. 1.7) at 140° for 2 hr.[92]; D, chromatography of the amino acids obtained by total hydrolysis of the remaining peptide.

Step 1, method A: The spot showed the characteristic pink center of PTH-threonine. As PTH-3-hydroxypipecolic acid has the same R_f value,[11] its presence could not be demonstrated. Method B gave threonine (+), glycine (++), alanine (+), α-aminobutyric acid (++) and 3-hydroxypipecolic acid (+). Method D showed that 3-hydroxypipecolic acid and threonine had been removed.

Step 2: Several spots were present (method A). Method B gave α-aminobutyric acid and phenylglycine. Method C gave the same amino acids and another spot, probably iodopipecolic acid. The hydrolysis of the peptide gave only proline and N-methyl-phenylalanine (method D).

Step 3: Method C gave proline and method D, N-methylphenylalanine.

(90) A thorough discussion of the method has been given by H. Fraenkel-Conrat in D. Glick, "Methods of Biochemical Analysis," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1955, p. 383

(91) Sjöquist, *Acta Chem. Scand.*, **7**, 447 (1953).

(92) D. F. Elliott and W. S. Peart, *Biochem. J.*, **65**, 246 (1957).

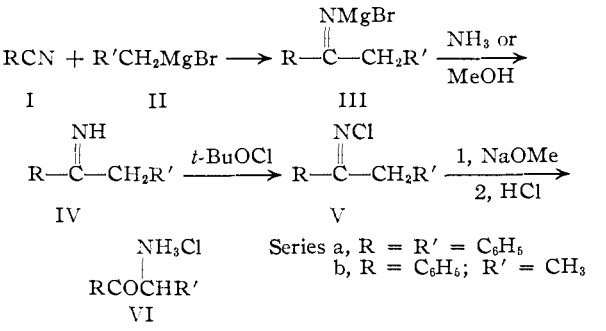
LOUVAIN, BELGIUM

COMMUNICATIONS TO THE EDITOR

REACTIONS OF AMINES. VI. SYNTHESIS OF α-AMINO KETONES AND ACIDS FROM IMINO DERIVATIVES[1,2]

Sir:

In earlier communications it has been shown that α-amino ketones may be prepared in good yields by the base catalyzed rearrangement of N,N-dichloro-*sec*-alkylamines.[1,3,4] We now report the modification of this synthesis as indicated in the charts to permit the preparation by sequence I → VI of α-amino ketones or by sequence VII → XIII of α-amino acids (or their esters) in 20–60% over-all yield from the corresponding nitriles.



With respect to the α-amino ketone sequence, Campbell[5] already has described the preparation of benzyl phenyl N-chloroketimine (Va) by a very similar sequence of reactions, although in his attempts to cause the further reaction of Va with base, he unfortunately chose to employ aqueous bases and thereby failed to complete the sequence.

(1) Paper V, THIS JOURNAL, **82**, 459 (1960).

(2) This work was supported in part by grants G-3689 and G-11339 of the National Science Foundation.

(3) H. E. Baumgarten and F. A. Bower, THIS JOURNAL, **76**, 4561 (1954).

(4) G. H. Alt and W. S. Knowles (*J. Org. Chem.*, in press) have reported the isolation of the intermediate N-chloroketimine in the base-catalyzed rearrangement of N,N-dichlorocyclohexylamine and the subsequent rearrangement of the former to α-aminocyclohexanone.

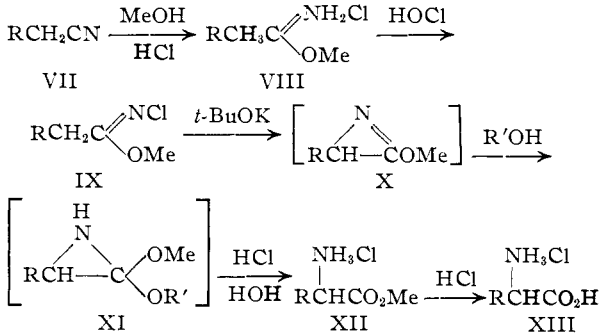
(5) K. N. Campbell, THIS JOURNAL, **59**, 2058 (1937).

We have repeated Campbell's experiments obtaining a 57% yield of benzylphenylketimine hydrochloride. This material was converted to the free ketimine (IVa) by treatment with ammonia and the IVa was chlorinated and treated with methanolic sodium methoxide without isolation of either IVa or Va following the procedure reported previously[1] but using one-half the quantities of *t*-butyl hypochlorite and sodium methoxide. From the acidification of the reaction mixture with hydrochloric acid, desylamine hydrochloride was obtained in 66% yield, a yield that compared quite favorably with the 45% yield obtained from the rearrangement of N,N-dichloro-1,2-diphenylethylamine.[1]

By a procedure similar to that described previously[1] the azirine (or aziridine) intermediate in the rearrangement reaction was reduced with lithium aluminum hydride to form *cis*-2,3-diphenylethylenimine in 48% yield (based on the hydrochloride of IVa).

These two experiments taken together and with that of Alt and Knowles[4] would appear to establish fairly definitely that both the N-chloroketimine and the azirine (or some closely related aziridine derivative) are intermediates in the rearrangement of N,N-dichloro-*sec*-alkylamines.

Ethylphenylketimine (IVb) was prepared from the reaction of ethylmagnesium bromide with benzonitrile in approximately 65% yield[6] and subjected to the halogenation and rearrangement reactions, giving a 55% (36% over-all) yield of α-aminopropiophenone hydrochloride (VIb).



In the α-amino acid sequence a substituted acetonitrile (VII) is converted to the methyl imino ester hydrochloride (VIII); VIII is halogenated with aqueous hypochlorous acid to the N-chloroimino ester (IX), and IX is subjected to base-catalyzed rearrangement, possibly proceeding through the azirine (X) or aziridine (XI) intermediates, and subsequent acid hydrolysis to the methyl ester of the α-amino acid (XII). The considerable stability of the latter toward aqueous acid permits its isolation or, by more vigorous treatment, hydrolysis to the α-amino acid hydrochloride (XIII).

Although essentially the same reagents and conditions as described previously[1] could be used, best results were obtained when each step (except XII → XIII) was performed at ice-bath temperatures. This change necessitated the use of potassium *t*-butoxide for all but the more reactive N-chloroimino esters.

Any of the unbracketed intermediates could be isolated and purified (with due care) if desired but no intermediate needed to be so purified between the initial reactant (VII) and the selected final product (VI or VII).

In a typical example, propionitrile was converted with methanol and hydrogen chloride into methyl iminopropionate hydrochloride (VIII, R = CH_3) in 94% yield. Chlorination of the imino ester with aqueous hypochlorous acid[7] gave a crude chloroimino ester,[8] which was not purified but was rearranged by addition to a slight excess of potassium *t*-butoxide. Treatment of the rearrangement product with aqueous hydrochloric acid gave 58% (54% over-all) of methyl α-aminopropionate hydrochloride. Hydrolysis of the latter with hot hydrochloric acid gave alanine in 51% over-all yield.

Maximum over-all yields of other α-amino acids (as the hydrochloride) included: glycine, 51%, norvaline, 21%, leucine, 59%, phenylglycine,[9] 51%, and phenylalanine, 44%. In each instance the methyl ester could be obtained in yields about 4–5% higher than that for the acid. The yields in the rearrangement step (IX → X) varied from 51–70%.

(6) Prepared by a procedure modelled after that of P. L. Pickard and T. L. Tolbert (private communication). We are indebted to Dr. P. L. Pickard for access to some of his unpublished results.

(7) Prepared from chlorine and a slight *excess* of aqueous sodium hydroxide.

(8) Chloroimino esters of the type described here show a strong band at about 6.2μ in the infrared spectrum and at most a weak band at 5.7μ (due to contamination by carboxylate ester).

(9) Sodium methoxide was used in place of potassium *t*-butoxide.

HENRY E. BAUMGARTEN
AVERY LABORATORY JERALD E. DIRKS
UNIVERSITY OF NEBRASKA JAMES M. PETERSEN
LINCOLN 8, NEBRASKA DONALD C. WOLF

RECEIVED JUNE 21, 1960

SYNTHESIS AND CHARACTERIZATION OF *CIS* AND *TRANS*-DICHLOROBIS-(ETHYLENEDIAMINE)-RHODIUM(III) SALTS:[1]

Sir:

We wish to report the synthesis and characterization of *cis*- and *trans*-$[Rh(en)_2Cl_2]^+$ salts (en = $NH_2CH_2CH_2NH_2$). None of the previous attempts to prepare geometrical and optical isomers of the dichlorotetramminerhodium(III) type had been successful. For example, salts of the complex ions $[Rh(NH_3)_4Cl_2]^+$,[2] $[Rh(en)_2Cl_2]^+$,[3] $[Rh(py)_4Cl_2]^+$,[4] $[Rh(bipy)_2Cl_2]^+$,[5] $[Rh(dien)_2Cl_2]^+$,[6] and $[Rh(en)(py)_2Cl_2]^+$[3] (py = pyridine, bipy = 2,2′-bipyridine, dien = $NH(CH_2CH_2NH_2)_2$) had been isolated in only one form and the structure of the particular isomer in each case was not established.

That these isomers had not been obtained and characterized previously is somewhat surprising

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract No. AF 49(638)315. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) W. W. Lebedinski, *Izvestija Inst. Izučeniju Platiny*, **12**, 74 (1935).

(3) J. Meyer and H. Kienitz, *Z. anorg. Chem.*, **242**, 281 (1939).

(4) S. M. Jörgensen, *J. prakt. Chem.*, **227**, 478 (1885).

(5) F. M. Jaegar and J. A. van Dijk, *Z. anorg. Chem.*, **227**, 273 (1936).

(6) F. G. Mann, *J. Chem. Soc.*, 469 (1934).