

These hydrolysis runs, with and without the presence of added inhibitor, were carried out in the phosphate buffer (pH 7.0) as previously described.² All inhibitor dilutions and acetylcholine solutions were freshly prepared before use in the standard sequence of kinetic determinations (at 25.12°) employing a series of inhibitor concentrations varying over the range of $1-10 \times 10^{-7}$ M.

The Wilson plot of v/v_1 vs. concentration for each of the inhibitors III and IV was linear over this concentration range, with least squares fits of about $\pm 6\%$ paralleling the observed magnitudes of precision of the slopes of individual rate plots. The velocity values v were obtained as the slopes of these rate plots for the first six to seven minutes of reaction, corresponding to about 10% completion of AC hydrolysis.

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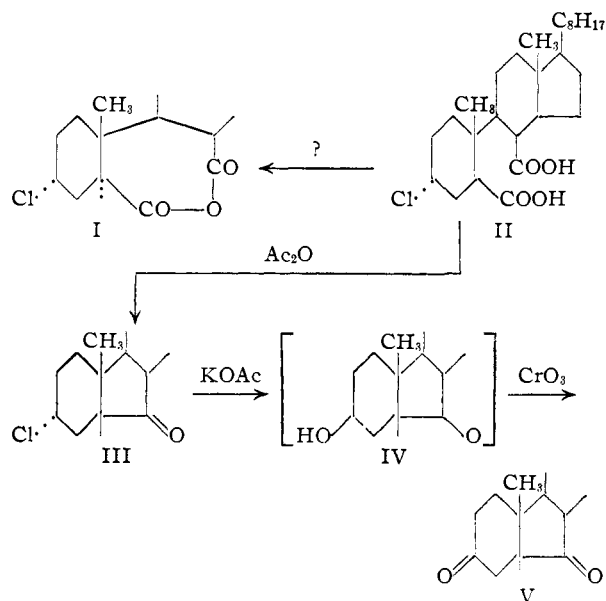
3 α -Chloro-B-norcoprostane-6-one

BY MARCEL GUT

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A few years ago we were interested in preparing 3 α -chloro-6,7-secocholestane-6,7-dioic acid anhydride (I). Windaus and Stein¹ reported that 3 α -chloro-6,7-secocholestane-6,7-dioic acid (II)² formed a crystalline anhydride melting at 187°. No further data on this compound were reported. A re-examination of this reaction produced a substance of the indicated melting point, the structure of which was, however, established to be 3 α -chloro-B-norcoprostane-6-one (III). Therefore, this ring closure proceeded according to Blanc's rule.³

In a recent publication Fieser⁴ reinterpreted Butenandt's oxidation and subsequent ring closure of 3,6-diketocholestene yielding B-norcoprostane-3,6-dione (V).^{4,5} This prompted us to transform the chloro analog into the known diketone V. The chloro compound III obtained by the ring closure was easily transformed into V and its identity es-



- (1) A. Windaus and G. Stein, *Ber.*, **37**, 3699 (1904).
- (2) At that time designated as 3 β -chlorocholestane-6,7-dicarboxylic acid.
- (3) H. G. Blanc, *Compt. rend.*, **144**, 1356 (1907).
- (4) L. F. Fieser, *THIS JOURNAL*, **75**, 4386 (1953).
- (5) A. Butenandt and E. Hausmann, *Ber.*, **70**, 1154 (1937).

tablished by comparison with authentic material.⁶ 3 α -Chloro-B-norcoprostane-6-one (III) was converted under conditions employed by Marker⁷ in similar cases to 3-hydroxy-B-norcoprostane-6-one (IV) (mainly the β -epimeride⁸) and the crude mixture was oxidized with chromic anhydride to the known B-norcoprostane-3,6-dione (V).

Experimental

A solution of 500 mg. of 3 α -chloro-6,7-secocholestane-6,7-dioic acid (II) in 15 ml. of acetic anhydride was heated on a steam-bath for 2 hours. Then the mixture was poured into ice, let stand for 2 hours, the solids filtered off, and finally recrystallized from methanol and dried; yield 215 mg., m.p. 180–183°. After sublimation at 140° (0.01 mm.) and recrystallization from acetone the melting point rose to 184–186°, $\alpha_D +10.3^\circ$ Chf (c 0.58).

Anal. Calcd. for C₂₆H₄₈OCl: C, 76.71; H, 10.65; Cl, 8.71. Found: C, 76.72; H, 10.54; Cl, 8.60.

Treatment of 100 mg. of the above ketone and 450 mg. of potassium acetate in 3 ml. of valeric acid under the same conditions as used by Marker, *et al.*,⁷ gave crude 3-hydroxy-B-norcoprostane-6-one (IV), which was oxidized with chromic anhydride in acetic acid. The resulting mixture gave after chromatographing 11 mg. of B-norcoprostane-3,6-dione (V),^{4,5} m.p. 114–116°. The diketone could not be isomerized with alkali and the melting point was unchanged after admixture of authentic material.⁶ The infrared spectrum shows two carbonyl bands at 5.76 and 5.81 μ .

Acknowledgment.—Thanks are due to the Damon Runyon Fund, U. S. Public Health Service (Grant No. C321) and to the American Cancer Society for an institutional grant which made this research possible.

(6) Obtained through the courtesy of Dr. L. F. Fieser.

(7) R. E. Marker, F. C. Whitmore and O. Kamm, *THIS JOURNAL*, **57**, 2358 (1935).

(8) C. W. Shoppee, *J. Chem. Soc.*, 1032 (1948).

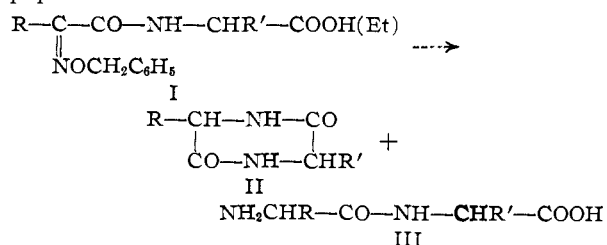
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Synthesis of Peptides via α -Benzoyloximino Acids¹

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Weaver and Hartung³ found that catalytic hydrogenation of N-benzoyloximinoacylamino acids or their esters, I, in acidic media produced predominantly diketopiperazines, II. Nevertheless, the formation of small amounts of the dipeptide, III, indicated that under other conditions compounds of structure I may prove useful in the synthesis of peptides.



In the earlier conversion of oximes into primary amines acidic media were always employed.⁴

(1) No. 14 in amino acid series; for no. 13 see J. H. R. Beaujon and W. H. Hartung, *THIS JOURNAL*, **75**, 2499 (1953).

(2) University of North Carolina, Chapel Hill, North Carolina.

(3) W. E. Weaver and W. H. Hartung, *J. Org. Chem.*, **15**, 741 (1950).

(4) W. H. Hartung, *THIS JOURNAL*, **53**, 2248 (1931).

Recently it has been observed that under certain conditions and for some oximino substrates an alkaline medium may be used without disadvantage.⁵ It was felt that reduction of compounds of type I in an ammoniacal solution might obviate the formation of the unwanted diketopiperazines, II, and afford better yields of the desired peptide III. The results were altogether favorable. Also it was found that the dipeptide may be readily isolated by simply volatilizing the solvent, after removal of the catalyst, and drying the product, for the salts readily lose ammonia under these conditions, leaving the substantially pure carboxylic acid derivative.

Experimental

The N-(α -benzyloximinoacyl)-amino acids were prepared substantially after procedures already described.^{3,6} A typical hydrogenation experiment was carried out as follows.

To a solution composed of 100 ml. of water and 3 ml. of concentrated ammonia was added 3.5 g. (0.013 mole) of N-(α -benzyloximinopropionyl)-DL-alanine and 3 g. of 10% palladium-charcoal catalyst. The mixture was shaken on a Parr apparatus at about 4 atm. pressure of hydrogen. After an hour, when the calculated hydrogen had been taken up, no further drop in pressure was observed. The catalyst was removed. About 1 ml. of the filtrate was acidified and formed a clear solution, indicating complete reduction. The remainder of the filtrate, in which the odor of toluene was pronounced, was evaporated over a steam-bath and at reduced pressure. The crystalline residue weighed 1.9 g., 90% of theory, gave no test for the ammonium ion and melted 277–278°. Fischer and Kautsch⁷ report for alanylalanine the m.p. 278°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: N, 17.5. Found: N, 17.0, 17.1.

Other peptides similarly prepared from appropriate intermediates are DL-phenylalanyl-glycine,⁸ m.p. 271–273°; DL-phenylalanyl-L-leucine,⁸ m.p. 225–227°; and DL-phenylalanyl-glycyl-glycine,⁹ m.p. 233–236°.

(5) W. H. Hartung and Y.-T. Chang, *THIS JOURNAL*, **74**, 5927 (1952).

(6) K. L. Waters and W. H. Hartung, *J. Org. Chem.*, **12**, 469 (1947).

(7) E. Fischer and K. Kautsch, *Ber.*, **38**, 2376 (1905).

(8) E. Fischer and P. Blank, *Ann.*, **354**, 9 (1907).

(9) F. Sigmund and F. Wesseley, *J. Physiol. Chem.*, **157**, 91 (1926).

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The Preparation of Dialkyl Zinc Compounds

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During the course of some studies on the reaction of organometallic compounds with monochloromethyl ether considerable difficulty was encountered in the preparation of organozinc compounds. The attempted preparation of dialkyl zinc compounds by the reaction of a mixture of an alkyl iodide and bromide with a zinc-copper couple often resulted in low yield or in failure. Dialkyl zinc compounds may be prepared by several methods the most common being the action of an alkyl iodide on (1) a mixture of zinc dust and copper prepared by the reduction of cupric oxide by hydrogen in the presence of the zinc and (2) an alloy prepared by blending molten zinc and copper. This alloy is usually

(1) Taken in part from the thesis submitted by P. J. C. T. in partial fulfillment of the requirements for the M.S. degree.

lathed into turnings and used as such. We have found that an apparently much more reactive zinc-copper couple can be prepared easily from zinc dust and cupric citrate by heating the mixture in an atmosphere of nitrogen to decompose the salt to copper. A comparison of the couples on the basis of simplicity of preparation, length of the induction period of the reaction with the halides, and the yields of the dialkyl zinc compounds obtained indicates the superiority of the new method for small scale laboratory preparations. In the following discussion the zinc-copper couple prepared by method (1) will be referred to as type A, the alloy as type B, and that by the new method as type C.

Type A is somewhat hazardous to prepare as it involves the heating of zinc dust and cupric oxide in an atmosphere of hydrogen just below the point of fusion of the mixture. In this Laboratory the mixture was found to be difficult to reduce completely. A trace of water was often observed in the reaction flask after a prolonged period of reduction. Type B couple involves the operations of melting, casting and latheing and is not practical for a few small scale experiments. Type C couple is made simply by heating with a free flame a mixture of zinc dust and cupric citrate below the point of fusion. The mixture is ready for use in 10–30 minutes depending upon the rate of heating.

The attempted reaction of the alkyl halide with the type A couple usually involved an induction period of one hour or longer while type B couple reacted within about 10 minutes. The reaction with type C couple in some cases was almost instantaneous and less than 10 minutes in all cases studied.

Using the type C couple diethylzinc was prepared in yields of 70%. This figure is below the value of 86–89% crude diethylzinc as given by Noller.² Using type A or type B couple dimethylzinc was prepared in this Laboratory in 60% yield. The work has been extended to the preparation of di-*n*-propyl- and di-isopropylzinc with the yields slightly above those obtained using the type B couple. In all cases the reaction was much more vigorous with the type C couple, and this couple gave easily reproducible results. Such was not the case with the type A couple where five runs were successful out of eleven attempts.

Experimental

The zinc dust was used directly as obtained from the J. T. Baker Chemical Co. The type A and type B couples were prepared according to the procedure of Noller.² The type C couple was prepared by mixing 130 g. of zinc dust with 25 g. of cupric citrate powder in a 500-ml. three-necked flask. The contents of the flask were heated over a free flame with occasional shaking under a protective current of dry nitrogen until all the cupric citrate had decomposed. This reaction was believed to be complete when moisture and other gases ceased to be evolved. Furthermore, the powder changed in appearance from a green color to a rust color. The mixture was then ready for use.

A 500-ml. three-necked flask containing the couple was equipped with a reflux condenser, a sealed stirrer and a dropping funnel. The apparatus was thoroughly flushed with nitrogen and warmed on a water-bath. Half a mole each of the alkyl bromide and iodide (purified) was placed in the funnel. A few milliliters of the solution were added to the flask and the remainder was added dropwise over a

(2) C. R. Noller, "Org. Syn." Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 184–187.