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

Ketimines. IV. From Fencholonitrile[1]

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The nitrile of fencholic acid has been treated with five Grignard reagents and the products described. The ketimines, with the exception of the one prepared using isopropylmagnesium bromide, were reduced to primary amines and hydrolyzed to ketones.

Previous studies in this Laboratory[2] have shown that *o*-tolyl *t*-butyl ketimine is stable to hydrolysis, while other alkyl aryl ketimines hydrolyze with varying degree of ease. The six isomeric ditolyl ketimines have also been shown to undergo hydrolysis.

To discover a possible relationship between structure and stability to hydrolysis, ketimines from fencholonitrile (1-methyl-3-isopropylcyclopentane nitrile) were prepared. This nitrile is isomeric with 2,2,6-trimethylcyclohexane nitrile, which has been shown to produce stable ketimines with either methylmagnesium iodide or phenylmagnesium bromide.[3]

The nitrile was prepared from commercial fencholic acid[4] by the usual sequence of reactions. In the preparation of the amide an oily by-product appeared which displayed characteristics of an amidine.

The imines were obtained from the nitrile and Grignard reagents made from isopropyl, *n*-butyl, isobutyl, *s*-butyl, isoamyl and phenyl bromides. Each ketimine was prepared several times, the ratio of Grignard reagent to nitrile being varied from 4.85 to 2 without any outstanding change in yield.

Isopropyl 1-methyl-3-isopropylcyclopentyl ketimine was recovered unchanged after refluxing two days with 6 *N* hydrochloric acid; it could not be reduced at atmospheric pressure over Adams catalyst. All the other ketimines hydrolyzed in dilute acid and reduced catalytically. The picrates, benzoates and benzenesulfonamides of the imines and amines were uncrystallizable oils. Attempts to prepare oximes, semicarbazones or 2,4-dinitrophenylhydrazones of the ketones were unsuccessful.

Experimental

Fencholyl Chloride.—Fencholic acid (94 g.) was treated with excess thionyl chloride and heated carefully until no further evolution of hydrogen chloride was observed. The acid chloride (98 g.) distilled at 68–72° (4 mm.). Without further purification or characterization this product was used in the preparation of the amide.

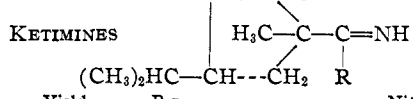
Fencholamide.—The acid chloride was dissolved in ether and anhydrous ammonia bubbled through the solution until no further reaction was observed. The ether was distilled at once and the residue washed with water and recrystallized from petroleum ether. The product was obtained in nearly quantitative yield and melted at 109°; calcd. for $C_{10}H_{19}NO$: N, 8.27; found: N, 8.21. When the amide was left in contact with ammonia in ether solution for five days before working up the product, oily crystals smelling of amidine were obtained. Washing with petroleum ether and evaporation of the solvent left a brown oil which could not be crystallized. A portion of it was treated with water with no apparent results. The water was poured off and replaced by 10% sodium hydroxide. Upon shaking the mixture a solid was formed which was proved to be the amide. Another portion of the oil was distilled. The evolution of ammonia was apparent and the condensate was found to be the nitrile. The amount of this oily by-product was found to increase with time when the amide was left in contact with the ether solution of ammonia. The pure amide was distilled but no nitrile could be obtained, indicating that the oil was not impure amide.

Fencholonitrile.—The amide was dissolved in an excess of phosphorus oxychloride and refluxed several hours. The mixture was neutralized with sodium bicarbonate solution, ether extracted, dried and distilled yielding the nitrile; b.p. 58–59° (1 mm.); d^{20}_4 0.8806; $n^{20}D$ 1.4434; calcd. for $C_{10}H_{17}N$: N, 9.27; found: N, 9.45. To characterize the nitrile further it was reduced over Raney nickel at 100 atmospheres of hydrogen, 4.0 g. of nitrile yielding 2.0 g. of 1-methyl-3-isopropylcyclopentylmethylamine[5]; b.p. 202–204°; d^{20}_4 0.8608; $n^{20}D$ 1.4550; benzoyl derivative m.p. 82°; benzenesulfonamide m.p. 112° (calcd. for $C_{16}H_{25}NSO_2$: N, 4.74; found: N, 4.65), picrate m.p. 161° (calcd. for $C_{16}H_{24}N_4O_7$: N, 14.57; found: N, 14.41).

Ketimines.—All preparations were by the method previously described.[2] The compounds are given in Table I.

TABLE I

KETIMINES



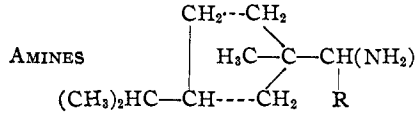
R	Yield, %	B.p., °C. (mm.)	d^{20}_4	$n^{20}D$	Nitrogen, % Calcd.	Found
Isopropyl[a]	47	93 (4)	0.8650	1.4691	7.17	6.99
n-Butyl	46	90–92 (1)	.8669	1.4639	6.69	6.63
Isobutyl	61	87–90 (2)	.8653	1.4635	6.69	6.85
s-Butyl	40	98–101 (3)	.8692	1.4651	6.69	6.40
Isoamyl	54	108–112 (3)	.8639	1.4649	6.27	6.26
Phenyl[b]	15	137–140 (1.5)	.9681	1.5255	6.11	6.07

[a] Benzenesulfonamide, m.p. 78°; calcd. for $C_{19}H_{29}NSO_2$: N, 4.17; found: N, 4.24. [b] Picrate, m.p. 279° (dec.) (calcd. for $C_{22}H_{26}N_4O_7$: N, 12.22; found: N, 12.20): hydrochloride, m.p. 137° (calcd., N, 13.36; found, 13.37).

Amines.—The ketimines were reduced in methanol over Adams catalyst at atmospheric pressure. In each case the

TABLE II

AMINES



R	B.p., °C. (mm.)	d^{20}_4	$n^{20}D$	Nitrogen, % Calcd.	Found
n-Butyl	92–93 (1)	0.8574	1.4620	6.63	6.55
Isobutyl	92 (1)	.8549	1.4609	6.63	6.86
s-Butyl	105–108 (3)	.8655	1.4674	6.63	6.87
Isoamyl	113 (3)	.8565	1.4624	6.21	6.32
Phenyl[a]	299–301 (735)	..	..	..	..

[a] Picrate, m.p. 177°; calcd. for $C_{22}H_{28}N_4O_7$: N, 12.17; found: N, 12.23.

(1) This paper is from a portion of a thesis presented in partial fulfillment of the requirements of the Degree of Doctor of Philosophy at the University of Oklahoma.

(2) P. L. Pickard, *et al.*, THIS JOURNAL, **72**, 876, 5017 (1950); **73**, 42 (1951).

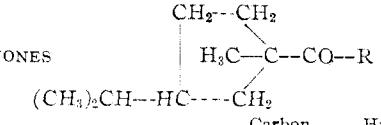
(3) H. L. Lochte, *et al.*, *ibid.*, **70**, 2012 (1948).

(4) Obtained from Dow Chemical Company.

(5) Wallach, *Ann.*, **379**, 199 (1911), reports this amine from the nitrile by reduction with sodium and alcohol, b.p. 204°, d^{20} 0.8500, $n^{20}D$ 1.4545, benzoyl derivative m.p. 81–82°.

TABLE III

KETONES



R	B.p., °C. (mm.)	d^{20}_4	$n^{20}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Butyl	97–99 (1)	0.8793	1.4543	79.93	79.95	12.46	12.46
Isobutyl	85–87 (1)	.8763	1.4527	79.93	79.53	12.46	12.34
s-Butyl	104 (6)	.8791	1.4539	79.93	79.59	12.46	12.37
Isoamyl	120–122 (6)	.8769	1.4544	80.29	80.26	12.58	12.44
Phenyl[a]	..	..	..	..	..	..	..

[a] The amount of the phenyl ketimine on hand was insufficient to prepare an isolable quantity of the ketone. A few milligrams of the imine was hydrolyzed and the product yielded a 2,4-dinitrophenylhydrazone, m.p. 138°, calcd. for $C_{22}N_{26}N_4O_4$: N, 13.65; found: N, 13.50.

hydrogen uptake was the calculated amount. Data on the amines are given in Table II. Isopropyl 1-methyl-3-isopropylcyclopentyl ketimine could not be reduced.

Ketones.—Each of the ketimines was refluxed with 6 *N* hydrochloric acid for three hours. The ketones were ether extracted, dried and distilled. The products are given in Table III. Isopropyl 1-methyl-3-isopropylcyclopentyl ketimine showed no signs of hydrolysis after 48 hours, being recovered quantitatively as the hydrochloride.

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[CONTRIBUTION FROM GARVERINÄRINGENS FORSKNINGSINSTITUT]

The Effect of Esterification of the Carboxyl Groups of Collagen upon its Combination with Chromium Compounds

BY K. H. GUSTAVSON

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In comparing the irreversible fixation of chromium complexes by intact collagen in the form of hide powder and by modified collagen with its carboxyl groups esterified by means of methanol, it is found that collagen loses its affinity for *cationic* chromium by the inactivation of the carboxylic groups. Since the methylated collagen fixes large amounts of *non-cationic* chromium complexes from solutions containing predominantly anionic and non-ionic chromium (sulfito-sulfato-chromium compounds), protein groups other than carboxyls must be involved in this type of reaction which probably is located to non-ionic protein groups (coördination). The lack of reactivity of the carboxyl ions of the ion exchange resin Amberlite IRC-50 for solutions containing non-cationic chromium solely provides further evidence for the interpretation of the fixation of the various chromium complexes given, *i.e.*, the carboxyl ions of collagen are responsible for the binding of electro-positive chromium complexes, whereas the combination of non-ionic and electronegative complexes with collagen is located to protein groups other than the carboxyls, probably by coördination on peptide links and hydroxy groups.

Introduction

Modern investigations of the important reaction of collagen with basic chromium salts, which has been extensively studied from the point of view of the chrome tanning process,[1] indicate the carboxyl ions of collagen to be specific for its irreversible binding of cationic chromium complexes. The initially ionic linking of the electropositive chromium complex to the anionic protein groups (carboxyl) is probably changed into a covalent–coördinate bond by the penetration of the carboxyl group into the complex, establishing direct multipoint attachment of the polynuclear chromium complex to the carboxyl groups of adjacent peptide chains (multipoint cross-linking). The great stability of the chrome–collagen compound formed and many other facts regarding its behavior are in harmony with this concept.[2] As to the mechanism of the binding of non-cationic chromium complexes by collagen, evidence for the function of groups other than the carboxyl in this reaction has been presented.[3] However, it has been postulated that the carboxyl group is instrumental for the fixation of chromium compounds generally, irrespective of their electrochemical state.[4]

It has earlier been demonstrated[5] that by complete discharge of the carboxyl ions of collagen by H ions (at *p*H 1.0), its fixation of cationic chromium complexes from dilute solutions of basic chlorides and sulfates of chromium is completely blocked. However, this method is limited to the low *p*H mentioned. By permanent inactivation or blockading of the carboxyl groups, for instance by their esterification, investigation of these reactions in a more desirable *p*H range, such as *p*H 2.5–5.0, should be feasible.

Esterification of collagen by means of methyl sulfate and methyl bromide has been attempted by Bowes and Kenten.[6] In view of the non-specificity of these agents for the carboxyl group and the marked hydrolytic breakdown of the protein incurred by the large number of treatments necessary for complete esterification, precaution must be taken in interpretation of the data. The methylating agents mentioned as well as diazomethane have been found unsuitable. The most promising method appears to be esterification by means of methanol in the presence of small amounts of hydrochloric acid, according to the procedure of Fraenkel-Conrat and Olcott[7] originally devised for globular proteins. This method has been employed in the present investigation.

Experimental

Esterified Hide Powder.—Twenty grams of collagen in the form of acetone-dehydrated hide powder (18.0% N) was shaken intermittently for 7 days in 2 l. of methanol made 0.1 *N* in respect to hydrochloric acid (15 ml. of concentrated

(1) For a general survey, see K. H. Gustavson, *Adv. Protein Chem.*, **5**, 353 (1949); S. G. Shuttleworth, *J. Soc. Leather Trades Chem.*, **34**, 410 (1950).

(2) K. H. Gustavson, *Adv. Protein Chem.*, **5**, 353 (1949).

(3) K. H. Gustavson, THIS JOURNAL, **48**, 2963 (1926); *J. Am. Leather Chem. Assoc.*, **42**, 201 (1947); G. Otto, *Leder*, **1**, 81, 133, 153 (1950).

(4) S. G. Shuttleworth, *J. Soc. Leather Trades Chem.*, **32**, 116 (1948); **34**, 410 (1950).

(5) K. H. Gustavson, *Svensk Kem. Tidskr.*, **52**, 75 (1940).

(6) J. H. Bowes and R. H. Kenten, *Biochem. J.*, **44**, 142 (1949).

(7) H. Fraenkel-Conrat and H. S. Olcott, *J. Biol. Chem.*, **161**, 259 (1945).