EXPERIMENTAL

α-Hydroxylamino nitriles. The data for these compounds are summarized in Table I. Typical syntheses are described.

Procedure A. With 14.0 g. of freshly distilled valeraldoxime (0.139 mole) was mixed 10 ml. of anhydrous hydrogen cyanide (0.2+ mole), and the mixture was allowed to stand for 2 days at room temperature. The solid was sucked dry on a Buchner funnel and washed with petroleum ether; it weighed 12.0 g. (67.7%).

Procedure B. To 21.0 g. of *n*-butyraldehyde (0.3 mole) was added a solution of 23.0 g. of hydroxylamine hydrochloride in 100 ml. water, and then with vigorous stirring was added over a period of 30 min. a solution of 15.2 g. of sodium cyanide (0.31 mole) in 50 ml. water. Stirring was continued for 3 days. The crystalline mass which had formed was sucked dry on a Buchner funnel, washed with a little water, and recrystallized from ether–petroleum ether solvent; 28.5 g. (75%).

Procedure C. Twenty grams of butyraldoxime (0.25 mole) was treated with 12.5 g. of sodium cyanide (0.25 mole) and 72 ml. of a saturated solution of sodium bisulfite; the solution was stirred at room temperature for 3 days. The crystalline mass was filtered off, washed with a little water, and recrystallized from ether–petroleum ether solvent; 25.8 g. (90.4%).

α-Hydroxylamino acids. The data for these are summarized in Table II. Typical experiments for their preparation are given.

Procedure D. A solution prepared from 10 g. of α-hydroxylamino nitrile and 60 ml. of concentrated hydrochloric acid was cooled in an ice bath and saturated with HCl gas, then allowed to stand at 0° for 1 day and at room temperature for 2 more days. The solution was then diluted with 40 ml. of water and refluxed for 6 hr. The water and hydrogen chloride were then removed on a steam bath and at reduced pressure to leave a residue of the α-hydroxylamino acid hydrochloride and ammonium chloride. The desired product was purified by either of two methods.

(1) The residue was taken up in water, decolorized with charcoal, filtered, and the *p*H of the solution was adjusted by the addition of ammonium hydroxide to between 6 and 7; after standing for a day in the refrigerator the solution deposited crystals which were collected on a Buchner funnel, washed with a little cold water, and crystallized from hot water to give colorless product.

(2) The residue was extracted with hot absolute ethanol and filtered; the filtrate was made basic with pyridine and allowed to stand for a day. The crystals were collected and purified as before.

Procedure E. A tenth gram-atom of sodium (2.3 g.) was dissolved in 140 ml. of absolute ethanol, and to the solution was added, with cooling, 5.0 g. of diethyl benzylmalonate (0.1 mole). Nitric oxide (generated by dropping concentrated sulfuric acid on aqueous sodium nitrite) was passed through the solution for 1 hr. and the reaction mixture allowed to stand at room temperature for 1 day. The alcohol was then volatilized at 30° at reduced pressure. To the residue was added 60 ml. of 20% sodium hydroxide solution (approximately 0.3 mole NaOH), allowed to stand at room temperature for a day, and the alkaline solution extracted with ether to remove any unchanged malonic ester. Then, keeping the temperature below 25°, dilute acid was added, and the oil which separated was boiled with 50 ml. concentrated hydrochloric acid for 15 min. The clear solution was cooled and with ammonium hydroxide the *p*H was adjusted to *p*H between 6 and 7. The crystalline colorless precipitate was collected on a Buchner funnel, washed with a little cold water, and then recrystallized from hot water; 10.0 g. (55.4%).

Reduction of α-hydroxylamino acids. Five grams of α-hydroxylaminovaleric acid in 30 ml. concentrated ammonium hydroxide solution, diluted by addition of 10 ml. water, was shaken on a Parr apparatus in hydrogen at four atmospheres pressure with 1 g. of palladium-charcoal catalyst. After 8 hr. the catalyst was filtered off, and the solution was evaporated to dryness; the residue weighed 3.5 g. The *N*-formyl derivative melted at 132–133°; reported 132°.[12]

In a similar manner β-phenyl-α-hydroxylaminopropionic acid was converted to β-phenylalanine, which was identified as its *N*-benzoyl derivative, m.p. 188–189°; reported 187–188°.[13] α-Hydroxylaminocaproic acid was reduced to α-aminocaproic acid, of which the *N*-formyl derivative melted at 115°; reported 113–115°.[14]

1-Hydroxylamino-1-cyclopentanecarboxylic acid was reduced to 1-amino-1-cyclopentanecarboxylic acid, hydrochloride salt, m.p. 222–224° (dec.) agreeing with the value observed for an authentic sample of the hydrochloride.[15] After hydrogenation, the product no longer reduced Fehling's solution or silver nitrate solution.

RICHMOND, VA.

(12) E. Abderhalden, *Chem. Zentr.*, **1921**, III, 296.
(13) E. Fischer and A. Mouneyrat, *Ber.*, **33**, 2383 (1900).
(14) D. Marko, *Ann.*, **362**, 333 (1908).
(15) L. Neelakantan, unpublished result.

[CONTRIBUTION FROM THE UNIVERSITY OF NORTH CAROLINA]

Methyl Ketone Isosters of α-Amino Acids[1]

KENNETH L. HOY[2] AND WALTER H. HARTUNG[3]

Received February 7, 1958

In the many correlations between the structure of organic compounds and their physiological activity the sequence of the four atoms $=N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-O-$ seems to be of considerable significance, for it appears in many substances exhibiting varied pharmacodynamic properties. Thus, compounds in which the oxygen atom appears as an alcoholic hydroxyl or its derivatives include acetylcholine, procaine, methantheline, epinephrine, chloroamphenicol, diphenhydramine, and the cinchona alkaloids, to name only a few. In the α-amino acids is found the same sequence, but with the terminal carbon as a carboxyl group; these are so numerous and of such importance as to constitute a specialized area in both organic and biological chemistry.

(1) Paper number 18 in the amino acid series. For number 17 see L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958).
(2) Present address: Union Carbide Chemicals Company, South Charleston, W. Va.
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Knowing the bond angles and employing Pauling's bond radii[4] one may calculate the distances between the oxygen and nitrogen atoms in this four-atom sequence for both the *cisoid* and *transoid* conformations. These values are given in Table I.

The biological activity of the amino alcohols and of the amino acids in which the $=N-\overset{|}{C}-\overset{|}{C}-O-$ sequence occurs suggests that in these compounds the distance between the N and the O atoms is optimum, permitting the compounds to lodge on the receptor site of the tissue. The particular site on which they lodge, that is, the characteristic reaction provoked in the tissues, is then determined by the nature and the magnitude of the substituents present in the $=N-\overset{|}{C}-\overset{|}{C}-O-$ grouping.

In the hypothetical oxidation of the amino alcohols to the amino acids the amino aldehydes, $=N-\overset{|}{\underset{|}{C}}-C=O$, and the amino ketones, $=N-\overset{|}{\underset{|}{C}}-C=O$, appear as intermediate stages and, according to the calculations given in Table I, they may also be expected to exhibit a high degree of physiological activity, since the distances between the N and O atoms, in both conformations, is similar to that for amino alcohols and amino acids. Again, the exact nature of the physiological response will be conditioned, it may be expected, by the substituents present in this four-atom grouping.

With these thoughts in mind, an exploratory investigation was undertaken for procedures which may be adapted for the synthesis of methyl ketones of general structure $R-\underset{|}{\underset{NH_3Cl}{CH}}-CO-CH_3$, which may be regarded as structural isosters of the α-amino acids. The experimental work is summarized schematically as follows:[5]

(4) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, 2nd ed., Ithaca, 1945, Chapter V.

(5) Many such ketones are described in the chemical literature, and they were prepared by various procedures. It is not the purpose of this report to review the various methods of synthesis and comment on them. Some will be found in the references cited.

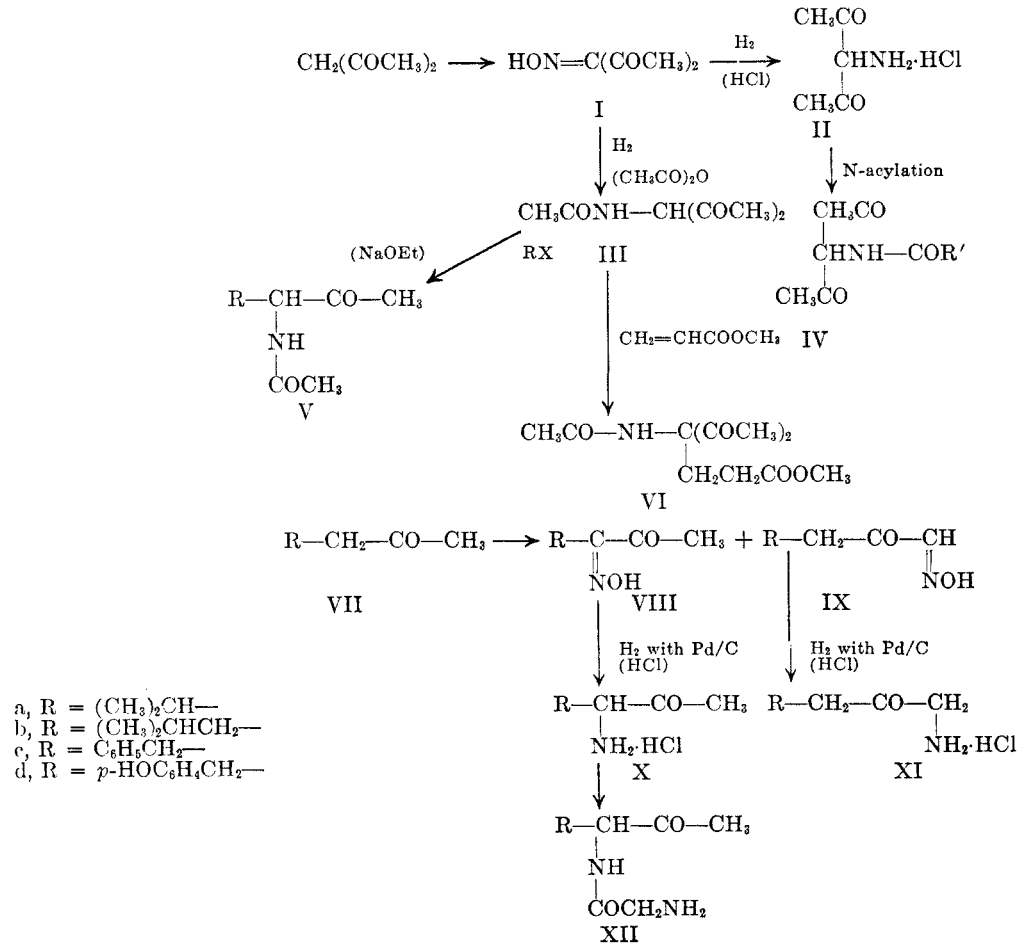


TABLE I

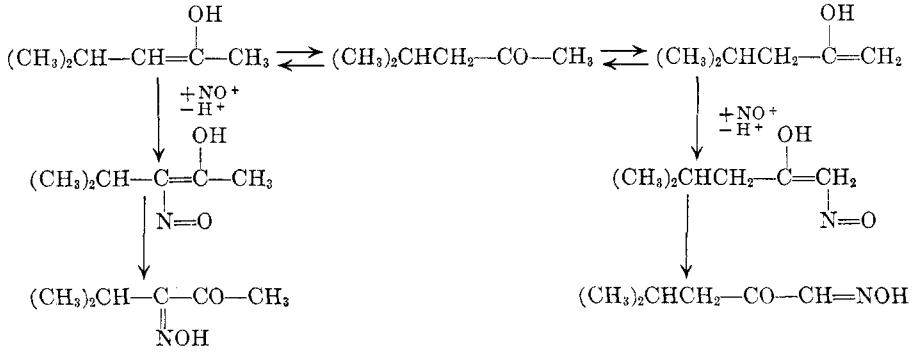
CALCULATED N TO O DISTANCES FOR VARIOUS MODIFICATIONS OF THE N—C—C—O SEQUENCES

Modification	Conformation	Distance between	A
=N—C—C—O	*Cisoid*	N and —O—	2.51
	Transoid		3.73
=N—C—C=O	*Cisoid*	N and =O	2.76
	Transoid		3.62
=N—C—C=O (with O below C)	*Cisoid*	N and =O	2.76
	Transoid		3.62
	Cisoid	N and —O—	2.51
	Transoid		3.73

The instability of the dipeptide analogs XIIa and XIIc, even in the form of their hydrochloride salts, was unexpected. This is undoubtedly a function of the amino group of the glycine moiety, along with the carbonyl group, for the intermediate carbobenzyloxy derivatives, from which they were prepared by hydrogenolysis, are quite stable. This suggests that a tripeptide analog will be more stable. The conversion of II to IV anticipates the formation of peptide-like compounds in which one terminal component is aminoacetone.

The formation of two isomeric oximino ketones during the nitrosation of 4-methyl-2-pentanone, VIIa, is probably typical for this reaction with all compounds of type VII. It was not established early enough to encourage the isolation of the isomers of type IX, except for IXa.

The results suggest that the nitrosation reaction is quite comparable to the bromination of such ketones in acidic media; and the proportion of the oximino isomers formed corresponds favorably with the analogous bromo isomers. It has been shown that bromination involves substitution on the enol form of the ketone.[6] For the formation of the oximino ketones the reaction then becomes as follows:



The nitrosoenolate, where possible will rearrange to the isomeric oximino ketone.[7]

(6) (a) P. D. Bartlett and C. H. Stauffer, *J. Am. Chem. Soc.*, **57**, 2580 (1935). (b) G. W. Wheland, *Advanced Organic Chemistry*, 2nd. ed. John Wiley and Sons, New York, 1951, p. 256.

(7) O. Touster, *Org. Reactions*, **VII**, 327–380 (1953).

EXPERIMENTAL

3-Oximino-2,4-pentanedione, I, was prepared by the procedure of Wolff and coworkers[8] in yields of 92% of theory. Crystallized from ligroin-benzene 1:6, it formed white crystals, m.p. 75–76°; reported m.p. 75°.[8]

Nitrosation of 4-methyl-2-pentanone, VIIa[9]. In a 500-ml. three-neck flask fitted with a sealed stirrer, dropping funnel, and a reflux condenser, was placed a solution of 50 g. (0.5 mole) of 4-methyl-2-pentanone in 300 ml. of dry ether and 50 ml. of anhydrous ethanol containing 0.00735 mole HCl/ml. Cooled to −5° there was added to the stirred solution 44.5 g. (0.5 mole) of freshly distilled isopropyl nitrite at such a rate that the color did not become darker than light orange and the temperature did not rise above 5°; stirring and cooling was continued for another 30 min., after which the reaction mixture was transferred to a one-liter separatory funnel and extracted with three 100-ml. portions of 10% sodium hydroxide solution. The combined alkaline extracts were cooled to 0° and slowly acidified with concentrated HCl to *p*H 3. On standing, an oily solid formed; this was collected on a Buchner funnel and pressed as dry as possible.

The solid was crystallized from ligroin; it weighed 32.0 g. (49.5%) and melted at 76–77° (reported m.p. 75°[10] and 76°[11]). A sample of the crystals treated with 2,4-dinitrophenylhydrazine formed orange colored prisms, which, crystallized from acetone and water, melted at 202°.

Anal. Calcd. for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.65. Found:[12] C, 46.22, 46.30; H, 4.75, 4.78; N, 22.4, 22.4.

The ligroin mother liquors from which the 4-methyl-3-oximino-2-pentanone had been crystallized contained a small amount of insoluble brown oil; this with the oil pressed from the crystals weighed 15.0 g. A sample of this crude oil treated with 2,4-dinitrophenylhydrazine formed red needles which, crystallized from acetone and water, melted at 234–235°. This was the dinitrophenylhydrazone of 4-methyl-1-oximino-2-pentanone (of IXa).

Anal. Calcd. for $C_{12}H_{15}N_5O_5$, C, 46.60%; H, 4.89%; N, 22.65%. Found:[12] C, 46.76, 46.56%; H, 4.33, 4.48%; N, 21.3, 21.2%.

Catalytic reduction of the crude oil in ethanolic HCl and the isolation of the hydrochloride of 4-methyl-1-amino-2-pentanone, m.p. 178–180°, described as m.p. 179–180°,[13] establishes this crude oil as consisting predominantly of 4-methyl-1-oximino-2-pentanone, IXa.

The nitrosation was repeated with 10.00 g. (0.100 mole) of 4-methyl-2-pentanone. After the reaction was complete, the solvent was volatilized. One hundredth of the residue, representing 0.001 mole, was treated with 2,4-dinitrophenylhy-

(8) V. Wolff, P. Block, G. Lorentz, and P. Trappe, *Ann.*, **325**, 134 (1902).

(9) This ketone was prepared by the reduction of mesityl oxide.

(10) B. Westenberger, *Ber.*, **16**, 2991 (1883).

(11) F. Lehmann, A. Bretscher, H. Kuhn, E. Sorkin, M. Erne, and H. Erlenmeyer, *Helv. Chim. Acta*, **33**, 1224 (1950).

drazine, depositing red-orange crystals; these, when dried, weighed 158.3 mg. and were taken up in 100.0 ml. of dioxane. Of this solution 10 ml. was passed through a column of alumina 2 cm. × 16 cm. previously washed with dioxane. The chromatogram, developed with dioxane, appeared as three distinct bands; each was separately eluted with 50% ether-dioxane. The product from the lowest band was identified as the 2,4-dinitrophenylhydrazone of 4-methyl-1-oximino-2-pentanone, m.p. 233–234°. The middle band comprised the dinitrophenylhydrazone of 4-methyl-3-oximino-2-pentanone, m.p. 200–203°. The top band was the 2,4-dinitrophenylhydrazone of unreacted 4-methyl-2-pentanone, m.p. 92–94°. The top product was not completely removed. As determined from a known mixture of the three dinitrophenylhydrazones, it was calculated that elution of the dinitrophenylhydrazones of the two oximino ketones afforded 94 to 96% recovery.

The separate eluates were isolated, taken up in 100 ml. of dioxane, and assayed by the transmittance of light at 3700 Å. On the basis of the data thus obtained, it is estimated that the ratio of nitrosation in the 1-position as compared to the 3-position is 1:3.

5-Methyl-3-oximino-2-hexanone, VIIIb, was prepared by the nitrosation of 5-methyl-2-hexanone, VIIb,[14] after the manner described by Aston and Mayberry[15] in a yield of 49%. It was isolated as a yellow oil, distilling at 90–97°/2 mm., which slowly formed crystals m.p. 40–42°; reported m.p. 42°.[16]

4-Phenyl-3-oximino-2-butanone, VIIIc, was isolated in 63% crude yield, 57% yield after crystallization from ligroin, as crystals m.p. 79–80°; reported m.p. 80–81°.[17] It was prepared by the nitrosation of 4-phenyl-2-butanone, VIIc,[18] according to the procedure employed by Hartung[19] for the preparation of α-oximinopropiophenone.

4-p-Hydroxyphenyl-3-oximino-2-butanone, VIIId, was prepared by similar nitrosation of 4-*p*-hydroxyphenyl-2-butanone, VIId[20]; after crystallization it melted at 122–126°, agreeing with the value reported by Sonn.[21]

DL-*3-Acetamido-2,4-pentanedione*, III. In a typical reduction a solution of 12.9 g. (0.1 mole) of 3-oximino, 2,4-pentanedione in 100 ml. of 98% acetic anhydride was shaken with 2 g. of A-100 catalyst[22] on a calibrated Parr apparatus with initial hydrogen pressure of 4 atmospheres. During 2 hr. 97.5% of the calculated H_2 was taken up. The catalyst was removed by filtration and the acetic anhydride–acetic acid solvent removed on a water bath at reduced pressure and at 80°. The residue was taken up in a small volume of benzene and forced out by the addition of ligroin, yielding 11.3 g. (72%); further crystallization gave white crystals m.p. 98–99°. With ferric chloride the product gave the red enol color characteristic for β-diketones. It was quite stable in boiling water.

Anal. Calcd. for $C_7H_{11}NO_3$: N, 8.92%. Found: N, 9.07, 8.94%.

DL-*3-Amino-2,4-pentanedione hydrochloride*, II, was obtained by the reduction of 3-oximino-2,4-pentandione with A-100 Pd/C catalyst according to established procedures. The product was white and crystalline, m.p. 161–162°.

Anal. Calcd. N for $C_5H_{10}NO_2Cl$; 9.24%, Found: 9.23, 9.55%.

The following were obtained by reducing the appropriate oximino ketones with catalysts of suitable potency, *i.e.*, A-100 to A-150, in ethanolic HCl as the solvent. The salts were isolated according to established procedures.

DL-*4-Methyl-3-amino-2-pentanone hydrochloride*, Xa. The salt melted with decomposition, never over more than a degree range, between 150° and 160°, depending on the rate of heating; previously reported m.p. 153.5–154°[23] and 150–151°.[24]

DL-*5-Methyl-3-amino-2-hexanone hydrochloride*, Xb. Crystals, m.p. 151–152°; previously reported 154–155°.[24]

DL-*4-Methyl-1-amino-2-pentanonehydrochloride*, XIa. Colorless crystals, m.p. (dec.) 178–180°; reported m.p. 179–180°.[13] Mixed with Xa m.p. ranged from 119° to 150°.

DL-*4-Phenyl-3-amino-2-butanone hydrochloride*, Xc. Crystals, m.p. 124–125°; previously reported m.p. 126–127°[25] and 130°.[21]

The Michael reaction with 3-acetamido-2,4-pentanedione. In a 300-ml. three-neck flask equipped with sealed stirrer, a reflux condenser, and a dropping funnel, was placed a solution of 120 ml. of absolute ethanol in which was dissolved 0.23 g. (0.01 mole) of metallic sodium. To this was added slowly and with stirring 31.4 g. (0.2 mole) of 3-acetamido-2,4-pentanedione. The solution was cooled to 0° and 17.2 g. (0.2 mole) of methyl acrylate was added at such a rate that the temperature of the reacting mixture did not rise above 10°; this required about an hour. Stirring was continued for 2 more hours and the mixture was then allowed to stand at room temperature for another day. It was then refluxed on a water bath for 2 hr. and acidified with glacial acetic acid to *p*H 6. The solvent was volatilized on a water bath at reduced pressure, leaving 31.0 g. of light oily residue, which after stirring and chilling solidified to crystals m.p. 113–114°; the product was 3-(β-carbomethoxyethyl)-3-acetamido-2,4-pentanedione, VI.

Anal. Calcd. for $C_{11}H_{17}NO_5$: N, 5.76. Found: N, 5.89, 5.80.

Ten grams of the crude product was refluxed for 2 hr. with 50 ml. of 10% HCl. After removal of the excess acid and water at reduced pressure on a water bath, the sirupy residue was taken up in a minimum of absolute ethanol; upon dilution with dry ether a salt weighing 5.5 g. (61%) was forced out; taken up in butyl alcohol and again forced out with ether, the crystals melted at 150–152°. A sample of the salt was benzoylated, forming 4-benzamido-5-ketohexanoic acid, m.p. 140–144°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: N, 5.61. Found: N, 5.54, 5.46%.

3-Phthaloylglycylamino-2,4-pentanedione (IV, R = $C_6H_4(CO)_2NHCH_2$—). The procedure employed is essentially that of Johnson and Nicolet,[26] using the amino-diketone II instead of an amino acid. From 3.58 g. (0.025 mole) of 3-amino-2,4-pentanedione hydrochloride and 8.92 g. (0.025 mole) of phthaloylglycyl chloride was obtained 7.2 g. (95% of theory) of product which, crystallized from acetone-water, melted 222–225°.

(12) Analyses by Messrs. Weiler and Strauss, Oxford, England.

(13) M. Jackman, M. Klenck, B. Fishburn, B. Tullar, and S. Archer, *J. Am. Chem. Soc.*, **70**, 2886 (1948).

(14) Prepared by hydrogenating isobutyralacetone with Pd/C catalyst.

(15) J. G. Aston and M. G. Mayberry, *J. Am. Chem. Soc.*, **57**, 1888 (1935).

(16) F. Treadwell and B. Westenberger, *Ber.*, **15**, 2788 (1882).

(17) D. G. Ponzio, *Gazz. chim. ital.*, **35**, 394 (1905).

(18) Prepared by hydrogenation of benzalacetone.

(19) W. H. Hartung, *J. Am. Chem. Soc.*, **50**, 5370 (1928).

(20) Prepared by the hydrolysis of ethyl *p*-hydroxybenzylacetoacetate.

(21) A. Sonn, *Ber.*, **40**, 4666 (1907).

(22) *Cf.* W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.*, **21**, 999 (1956). The symbol A-100 designates an *acetate* palladium-on-charcoal catalyst with 100 mg. $PdCl_2$ per gram of carrier.

(23) H. Dakin and R. West, *J. Biol. Chem.*, **78**, 745, 757 (1928).

(24) H. Erlenmeyer *et al.*, *Helv. Chim. Acta*, **33**, 1221 (1950).

(25) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **79**, 95 (1928).

(26) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 353 (1914).

Anal. Calcd. N for $C_{15}H_{14}N_2O_5$, 9.27%. Found: 9.18, 9.10%.

3-p-Nitrobenzoylamino-2,4-pentanedione (IV, R = *p*-$NO_2C_6H_4$—). From 5.87 g. (0.04 mole) of 3-amino-2,4-pentanedione hydrochloride and an equivalent amount of *p*-nitrobenzoyl chloride (7.7 g.) the amide was obtained in 92% yield. After crystallization from ethanol it melted 199–200°.

Anal. Calcd. N for $C_{12}H_{12}N_2O_5$: 10.61%. Found: 10.41, 10.45%.

4-Methyl-3-glycylamino-2-pentanone hydrochloride, XIIa. This compound was prepared by an adaptation of the mixed anhydride procedure for preparing amides described by Vaughan and Osato.[27] From 3.78 g. (0.025 mole) 4-methyl-3-amino-2-pentanone hydrochloride and 5.23 g. (0.025 mole) of carbobenzyloxyglycine was obtained 5.6 g. (71% of theory) of an oil which did not crystallize but did give a positive iodoform test. The crude product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in ethanolic HCl solvent. The product, weighing 3.5 g. (95% of theory) was a viscous hydroscopic oil which refused to crystallize even in vacuum over P_2O_5; it was insoluble in ether, gave a positive iodoform reaction, a positive test for Cl^- ion, and a positive biuret reaction. After several days evidence of decomposition could be observed. Upon benzoylation it formed a solid which, crystallized from benzene, melted 144.5–146°.

Anal. Calcd. for $C_{15}H_{20}N_2O_{30}$: N, 10.14. Found: N, 9.96, 10.18.

4-Phenyl-3-glycylamino-2-butanone hydrochloride, XIIc. From 5.97 g. (0.03 mole) of 4-phenyl-3-amino-2-butanone hydrochloride and 5.85 g. (0.03 mole) of carbobenzyloxyglycine was obtained 8.0 g. (76% of theory) 4-phenyl-3-(carbobenzyloxyglycylamino)-2-butanone, a slightly yellow solid; recrystallized from benzene-ligroin it melted 83.5–84.5°. The crystals gave a positive iodoform reaction.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: N, 7.91. Found: N, 7.82, 7.90%.

Three and a half grams of the product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in the presence of ethanolic HCl; the product weighed 2.5 g. (98% of calculated) and melted with decomposition at 141–142°. It was soluble in water but insoluble in ether; it gave a positive iodoform test and a positive test for the Cl^- ion. It discolored readily.

Anal. Calcd. for $C_{12}H_{17}N_2O_2Cl$: N, 10.91. Found: N 10.80, 10.77%.

Alkylation of 3-acetamido-2,4-pentandione. In a 500-ml. three-neck flask equipped with sealed stirrer, reflux condenser, and dropping funnel was placed a cold solution of 400 ml. of absolute ethanol containing 6.6 g. (0.1 mole) of sodium ethoxide and 15.7 g. (0.1 mole) of 3-acetamido-2,4-pentanedione; to the stirred solution was added over the period of an hour 13.6 g. (0.108 mole) of benzyl chloride. Stirring was continued for 4 additional hours, at which time the NaCl had separated and the reaction mixture become neutral to moist litmus. As much as possible of the solvent was removed at reduced pressure on a water bath, and to the residue was added 75 ml. of water. Two layers formed; the mixture was extracted with four 100-ml. portions of ether. Upon evaporation of the ether extracts 10.5 g. of a tan solid remained; upon recrystallization from 40% alcohol, 8.2 g. of 4-phenyl-3-acetamido-2-butanone was obtained. Further crystallization afforded product, m.p. 96.5–97°; reported m.p. 98–100°[23] and 95–95.5°.[28]

CHAPEL HILL, N. C.

(27) J. Vaughan and R. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(28) G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, WEST POINT, PA.]

Synthetic Antiviral Agents: II. Various Substituted 5-Oxopentanoic and 5-Oxohexanoic Acids and Certain of Their Derivatives[1]

EDWARD J. CRAGOE, JR., A. M. PIETRUSZKIEWICZ, AND C. M. ROBB

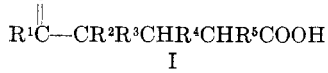
Received January 17, 1958

A number of substituted 5-oxopentanoic and 5-oxohexanoic acids, some of which showed an interesting order of antiviral activity, were prepared by the hydrolysis of the corresponding nitriles. 4,5-Diphenyl-5-oxopentanoic acid was obtained by the interaction of desoxybenzoin and β-propiolactone. 4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid was resolved through the cinchonine salt.

The intermediate 5-oxoalkanenitriles containing substituents in the 4 and/or 5 positions were produced by cyanoethylation of the appropriate ketones. 3,4-Diphenyl-5-oxohexanenitrile and 3,4,5-triphenyl-5-oxopentanenitrile were prepared by the action of cinnamonitrile on the appropriate ketone.

4-Phenyl-5-oxohexanamide was synthesized from 1-phenyl-2-propanone and acrylamide. Several derivatives, including three esters, the enol lactone and the corresponding hydroxy lactone of 4,4-diphenyl-5-oxohexanoic acid, are described.

Following the observation of antiviral properties of 4,4-diphenyl-5-oxohexanoic acid and 4-aryl-alkyl-4-aryl-5-oxohexanoic acids[2] a study of the properties of structurally related compounds was undertaken. There are many portions of the molecule where interesting structural variations could be made. However, it is the intent in this paper to



I

restrict the variations in Formula I mainly to examples where one R group is aryl, a second R is aryl, alkyl, or substituted alkyl and a third R is phenyl, methyl, or hydrogen, while the remaining R groups are hydrogen.

(1) A portion of the material contained in this paper was presented by the first two authors at the First Regional Meeting of the Delaware Valley Sections of the American Chemical Society, Feb. 16, 1956.

(2) E. J. Cragoe and A. M. Pietruszkiewicz, *J. Org. Chem.*, **22**, 1338 (1957).