Notes

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Shozo Kamiya and Kimie Koshinuma*1: Ring-substituted α-Amino Acids. II.*2 The Reaction of Cyclic Lactams with Methyl Vinyl Ketone leading to the α,γ-Diaminobutyric Acid Derivatives.

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In the preceding paper, it was shown that the addition reaction of maleic hydrazide derivatives with α,β-unsaturated carbonyl compounds gave the N-addition products, from which the corresponding α,γ-diaminobutyric acid derivatives were prepared in good yields.

The present paper describes the addition reaction of various cyclic lactams such as 2(1*H*)-quinolone, 1(2*H*)-isoquinolone or 1,2-benzisothiazolin-3-one-1,1-dioxide (saccharin) with methyl vinyl ketone leading to the corresponding hydantoins and α,γ-diaminobutyric acid derivatives as an extension of this series. These amino acids may be expected to show some biological activity in view of their structural relationship to mimosine and willardin.*2

Reaction of 2(1*H*)-quinolone (I) with methyl vinyl ketone in the presence of catalytic amount of sodium hydroxide produced a monoaddition product in 17% yield, along with the recovery of about half of the starting material. Upon the reaction in absolute ethanol in the presence of sodium methoxide, the same compound was isolated in 2% yield, recovering most of the starting material. When these reactions were tried in a sealed tube at higher temperature, only a large quantity of polymerized product was obtained.

It is well known that alkylation of 2(1*H*)-quinolone derivatives with alkyl iodides, dimethyl sulfate or diazomethane gives either an O- or N-alkyl derivative, or a mixture of both, depending on reaction conditions and the presence of substituents in the quinoline ring.

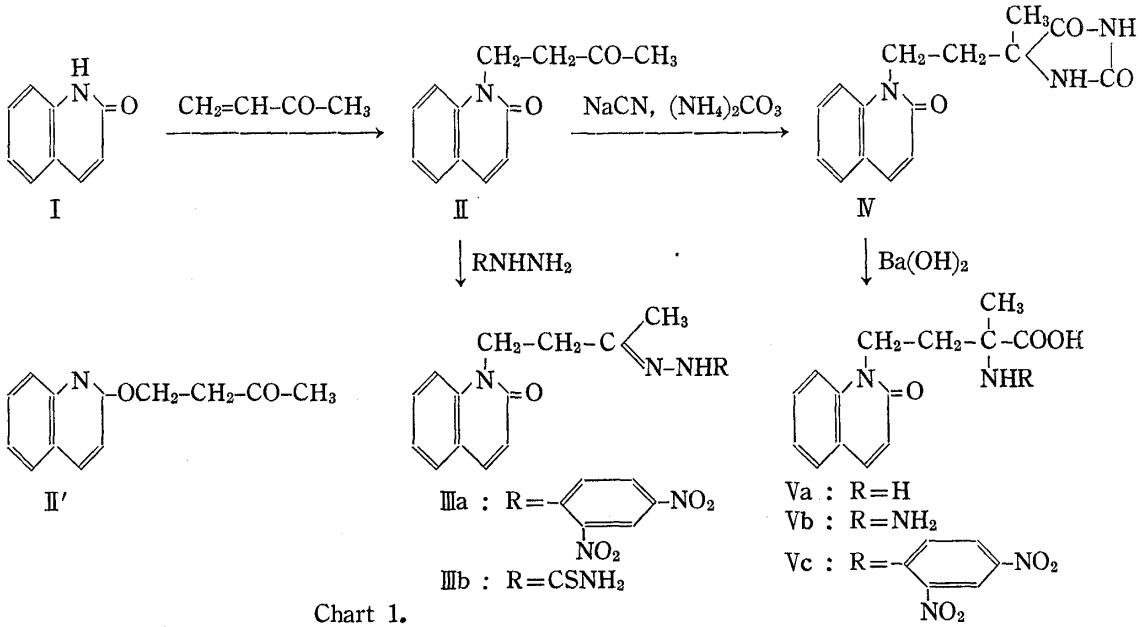

Chart 1.

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*2 Part I: This Bulletin, **15**, 949 (1967).

The infrared spectrum of the monoaddition product shows a lactam-type carbonyl function of the 2(1*H*)-quinolone ring at 1640 cm^{-1}, and lacks in the absorption due to a NH which is observable at 3240 cm^{-1} in that of I. In addition, its ultraviolet spectrum is quite similar both in form and in extinction to that of 1-methyl-2(1*H*)-quinolone as noted in the experimental part. Also, II formed the corresponding 2,4-dinitrophenylhydrazone (IIIa) and thiosemicarbazone (IIIb) in both almost quantitative yields. These facts indicate that the structure is not the O-addition product (II'), but the N-addition product, 1-(3-oxobutyl)-2(1*H*)-quinolone (II), as shown in Chart 1.

Analogously, the reacon of 1(2*H*)-isoquinolone (VI) with methyl vinyl ketone gave the N-addition product, 2-(3-oxobutyl)-1(2*H*)-isoquinolone (VII) in 72% yield. The structure of VII was also assigned from its infrared spectrum showing the ring carbonyl group at 1650 cm^{-1} as well as from the close similarity in ultraviolet spectra of the product and N-substituted 1(2*H*)-isoquinolones.

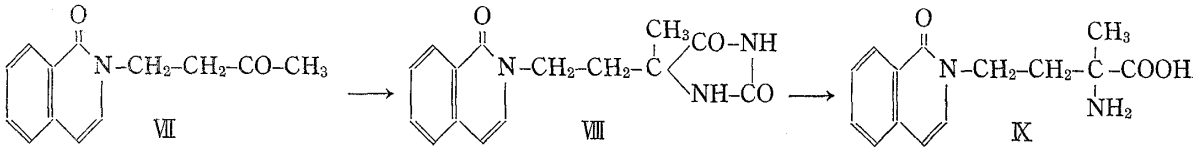


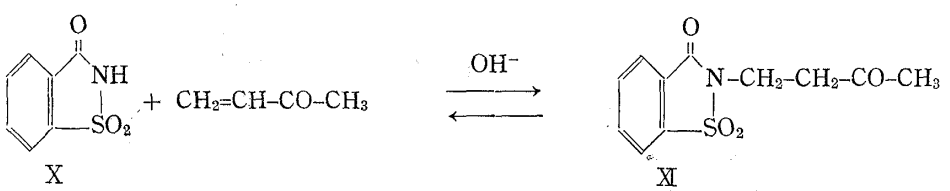
Chart 2.

The low yield of the product in the reaction of I with methyl vinyl ketone is contrast with VI which gives the N-addition product in 72% yield as mentioned above. Actually, the Mannich reaction, a similar reaction to this addition reaction, of such 2(1*H*)-quinolone derivatives as I, 3,4-dihydro-2(1*H*)-quinolone or 5,6,7,8-tetrahydro-2(1*H*)-quinolone resulted in recovery of the starting materials, but 3,4-dihydro-1(2*H*)-isoquinolone gave a N-Mannich base.[1] From these facts, it is considered that the low yield in the case of I is mainly due to steric hindrance by the hydrogen in the 8-position *peri* to the lactam-hydrogen rather than to a reversed reaction in which I and methyl vinyl ketone are regenerated.

Treatment of II with sodium cyanide and ammonium carbonate, followed by acidification gave the hydantoin (IV) in 76% yield. Subsequently, IV was hydrolyzed by heating with barium hydroxide to give DL-2-amino-2-methyl-4-(2-oxo-1(1*H*)-quinolyl)butyric acid (Va) in 35% yield. As usual α-amino acids, Va afforded the corresponding N 2,4-dinitrophenyl derivative (Vc) and the ester. Similarly, VII was converted to DL-2-amino-2-methyl-4-(1-oxo-2(2*H*)-isoquinolyl)butyric acid (IX) through the hydantion (VIII) by the Bucherer synthesis.

The Strecker synthesis of II using potassium cyanide and hydrazine hydrochloride gave 2-hydrazino-2-methyl-4-(2-oxo-1(1*H*)-quinolyl)butyric acid (Vb), but further purification was impossible owing to its remarkable hygroscopicity.

Reaction of 1,2-benzisothiazolin-3-one-1,1-dioxide (X), which has a lactam-hydrogen of another kind, with methyl vinyl ketone gave the N-addition product, 2-(3-oxobutyl)-1,2-benzisothiazolin-3-one-1,1-dioxide (XI) in 89% yield. Its infrared spectrum in nujol indicates a characteristic absorption band at 1730 cm^{-1} attributable to the lactam carbonyl. Since XI easily decomposed by a reversed reaction to regenerate X and methyl vinyl ketone under such an alkaline medium as in the Bucherer synthesis, the corresponding hydantoin



1) B. Reichert: "Die Mannich-Reaktion," 113 (1959), Springer-Verlag.

could not be obtained. On the other hand, the Strecker synthesis yielded a ninhydrin positive product, but further purification was impossible owing to its remarkable hygroscopicity.

The amino acids, Va and Ⅸ, produce blue color with ninhydrin, and their Rf values in paperchromatography (solvent system : *n*-butanol–acetic acid–water, 4:1:5) were observed to be 0.59 for Ⅳa and 0.64 for Ⅸ.

These amino acids did not show bacteriostatic activities bellow concentrations of 5000 μg./ml. against *Eschinichia coli*, *Staphylococcus aureus* and *Mycobacterium tuberculosis* 607. Their antitumor and other biological tests are under investigation, the results of which will be reported separately.

Experimental*3

1-(3-Oxobutyl)-2(1*H*)-quinolone (II)——A mixture of 11.02 g. (0.076 mole) of 2(1*H*)-quinolone,[2] 7.0 g. (0.10 mole) of methyl vinyl ketone, 100 ml. of ethanol and 5 drops of a 20% sodium hydroxide solution was refluxed for 3 hr. Additional 7.0 g. (0.10 mole) of methyl vinyl ketone was added, and the mixture was further refluxed for 3 hr. The reaction mixture was concentrated under reduced pressure, the separated crystals were filtered, and dried. Pale yellow needles, m.p. 197°. This compound was identical with starting material by mixed melting point determination. 5.20 g. (47% recovery). The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in chloroform, and the chloroform solution was extracted with a 5% sodium hydroxide solution twice. After washing with water, the chloroform was evaporated to dryness, the residue was dissolved in ether, and the ether solution was dried over anhyd. sodium sulfate. The ether solution was passed through an alumina column in order to separate the polymerized by-product. After washing the column with ether, the combined ether solution was evaporated to dryness, and the residue was dissolved in ethanol. A small amount of iso-propylether was added to the solution, and the mixture was allowed to stand in a refrigerator over three days. The separated crystals were filtered, washed with a mixture of ethanol and iso-propylether, and recrystallization from ethanol gave colorless needles, m.p. 85~88°. Yield, 2.80 g. (17%). IR ν_{max}^{KBr} cm^{-1} : 1702 (CO), 1640 (ring CO). UV λ_{max}^{EtOH} mμ (log ε) : 271 (3.85), 279 (3.83), 317 (3.72), 330 (3.80), 344 (3.65). 1-Methyl-2(1*H*)-quinolone, UV λ_{max}^{EtOH} mμ (log ε) : 271 (3.83), 279 (3.80), 318 (3.72), 330 (3.79), 344 (3.64). *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found : C, 72.60; H, 5.91; N, 6.64.

2,4-Dinitrophenylhydrazone (Ⅲa) : Yellow needles, m.p. 248~249° (decomp.) (from ethanol). *Anal.* Calcd. for $C_{19}H_{17}O_5N_5$: C, 57.72; H, 4.33. Found : C, 58.44; H, 4.53.

Thiosemicarbazone (Ⅲb) : Slightly yellow leaflets, m.p. 206° (decomp.) (from diluted acetic acid). *Anal.* Calcd. for $C_{14}H_{16}ON_4S$: C, 59.98; H, 5.73; N, 19.43. Found : C, 60.46; H, 5.63; N, 18.66.

The Hydantoin (IV) derived from 1-(3-Oxobutyl)-2(1*H*)-quinolone (II)——To a solution of 2.15 g. (0.01 mole) of Ⅱ and 3.0 g. of ammonium carbonate in 40 ml. of 50% ethanol was added dropwise a solution of 0.59 g. (0.012 mole) of sodium cyanide in 5 ml. of water with stirring. The solution was heated at 75~80° for 1.5 hr. on a water bath. Additional 0.8 g. of ammonium carbonate was added, and the mixture was heated again at 75~80° for 1.5 hr., during which time the excess ammonium carbonate was evaporated. The reaction mixture was concentrated under reduced pressure, and carefully acidified with 10% hydrochloric acid in a hood. The separated colorless powder was filtered, washed with cold water, and dried. Recrystallization from diluted ethanol gave 2.29 g. (80%) of the hydantoin, colorless leaflets, m.p. 251~252°. IR ν_{max}^{Nujol} cm^{-1} : 3260, 3060, 1768, 1720, 1695 (NH and CO of hydantoin). *Anal.* Calcd. for $C_{15}H_{15}O_3N_3$: C, 63.15; H, 5.30; N, 14.73. Found : C, 63.10; H, 5.48; N, 14.62.

DL-2-Amino-2-methyl-4-(2-oxo-1(1*H*)-quinolyl)butyric Acid (Va)——A mixture of 1.43 g. (0.005 mole) of the hydantoin and 3.16 g. (0.01 mole) of barium hydroxide octahydrate and 20 ml. of water was refluxed for 4 hr. After the reaction mixture was diluted with the same volume of water, nitrogen was passed through to exclude the ammonia which was produced during hydrolysis, and the reaction mixture was filtered. The filtrate was acidified with 20% sulfuric acid, the precipitated barium sulfate was filtered, and washed with water. The combined filtrate was passed through an Amberlite IR-120 (H-form) column, and the column was washed with water till no more sulfate ion was detected with a barium nitrate solution. The absorbed amino acid was eluted by passing a diluted ammonia solution (twenty ml. of conc. ammonia solution was diluted to 500 ml. with water). The elution of Va was checked by heating a few drops of the eluant with 0.2% ninhydrin ethanolic solution. The eluant was concentrated under reduced pressure until white flacks began to form. The residue was treated with ethanol, and the mixture was allowed to stand in a refrigerator overnight. The deposited crystals were filtered, washed with ethanol, and dried. Colorless powder, m.p.

*3 All melting points are uncorrected. Infrared and ultraviolet spectra were measured on a JASCO Model-IR infrared spectrophotometer, and on a Hitachi Model EPS-2 ultraviolet spectrophotometer.

2) E. Ochiai, T. Yokokawa : Yakugaku Zasshi, **75**, 213 (1955).

242°(decomp.) (from a mixture of methanol and ethanol). Ninhydrin reaction: blue. Yield, 0.68 g. (52%). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2 \cdot H_2O$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.58; H, 6.66; N, 10.09.

N-(2,4-Dinitrophenyl) derivative (Vc): Yellow granules (from ethanol), m.p. 252°(decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_7N_4$: C, 56.33; H, 4.26. Found: C, 56.49; H, 4.54.

Methyl ester hydrochloride: Slightly yellow granules, m.p. 221°(decomp.) (from a mixture of ethanol and iso-propylether). IR ν_{max}^{Nujol} cm^{-1}: 1760 (ester), 1650 (ring CO). *Anal.* Calcd. for $C_{15}H_{18}O_3N_2 \cdot HCl$: N, 9.01. Found: N, 9.05.

2-(3-Oxobutyl)-1(2*H*)-isoquinolone (VII)——A mixture of 3.48 g. (0.024 mole) of 1(2*H*)-isoquinolone prepared from 1-chloroisoquinoline,[3] 40 ml. of ethanol, 2.10 g. (0.03 mole) of methyl vinyl ketone and 3 drops of freshly prepared a 20% sodium hydroxide solution was refluxed for 2 hr. on a water bath. The reaction mixture was refluxed again with additional 2.10 g. (0.03 mole) of methyl vinyl ketone for 1.5 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue was extracted with chloroform, and the chloroform layer was extracted with a 5% sodium hydroxide solution twice. After washing with water, the chloroform layer was dried over anhyd. sodium sulfate, and the chloroform was evaporated to dryness. The syrupy residue was extracted with ether, the ether extract was passed through an alumina column, and the column was washed with ether. The combined ether eluant was evaporated to dryness, and the residue (a yellow, viscous liquid) was purified by distillation. Yellow, viscous liquid, $b.p._3$ 174~178°. IR $\nu_{max}^{Cap.}$ cm^{-1}: 1710 (CO), 1650 (ring CO). Yield, 3.71 g. (72%).

2,4-Dinitrophenylhydrazone: Red, crystalline powder (from methanol), m.p. 212~215°(decomp.). *Anal.* Calcd. for $C_{19}H_{17}O_5N_5$: C, 57.72; H, 4.33; N, 17.72. Found: C, 57.10; H, 4.36; N, 18.03.

The Hydantoin (VIII) derived from 2-(3-Oxobutyl)-1(2*H*)-isoquinolone (VII)——This compound was prepared from VII by the method similar to that used for the preparation of IV. Colorless granules (from methanol), m.p. 232~233°. IR ν_{max}^{Nujol} cm^{-1}: 3160, 1760, 1710 (NH and CO of hydantoin) and 1642 (ring CO). Yield, 89%. *Anal.* Calcd. for $C_{15}H_{15}O_3N_3$: C, 63,15; H, 5.30; N, 14.73. Found: C, 62.70; H, 5.17; N, 15.03.

DL-2-Amino-2-methyl-4-(1-oxo-2(2*H*)-isoquinolyl)butyric Acid (IX)——This compound was prepared from the hydantoin by the similar method that used for the preparation of Va in 40% yield. Colorless granules (from a mixture of methanol and ethanol), m.p. 257°(decomp.). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.52; H, 6.02; N, 10.61.

2-(3-Oxobutyl)-1,2-benzisothiazolin-3-one-1,1-dioxide (XI)——A mixture of 18.3 g. (0.1 mole) of benzisothiazolin-3-one-1,1-dioxide, 14.0 g. (0.2 mole) of methyl vinyl ketone, 100 ml. of ethanol and 5 drops of a 20% sodium hydroxide solution was refluxed for 4 hr. The reaction mixture was concentrated under reduced pressure, and the solution was allowed to stand in a refrigerator overnight. The separated crystals were filtered, washed with EtOH, and recrystallized from a mixture of EtOH and H_2O. Colorless prisms, m.p. 122~123°. IR ν_{max}^{Nujol} cm^{-1}: 1730 (ring CO), 1715 (CO). Yield, 24.6 g. (97%). *Anal.* Calcd. for $C_{11}H_{11}O_4NS$: C, 52.11; H, 4.39; N, 5.33. Found: C, 52.62; H, 4.35; N, 5.13.

2,4-Dinitrophenylhydrazone: Orange yellow leaflets, m.p. 188°. IR ν_{max}^{Nujol} cm^{-1}: 1730 (ring CO). *Anal.* Calcd. for $C_{17}H_{15}O_7N_5S$: C, 47.11; H, 3.48. Found: C, 47.05; H, 3.60.

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3) M. Ikehara: This Bulletin, **2**, 111 (1954).

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Hisashi Murata and Masahiro Mori*1: Distribution and Excretion of Benhepazone administered to Rats.

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In a previous experiment,[1] various kinds of metabolic products of Benhepazone (1-benzylcycloheptimidazol-2(1*H*)-one) was found in urine after its oral administration to

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1) H. Murata, A. Yasumura: Seikagaku, **37**, 461 (1965).