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132. Shiro Terashima, Kazuo Achiwa, and Shun-ichi Yamada: Chemistry of Amino Acids. II.*1 Studies on α-Alkyl-α-Amino Acids. I. Abnormal Decarbonylation of α-Methyl-α-phenylglycine.

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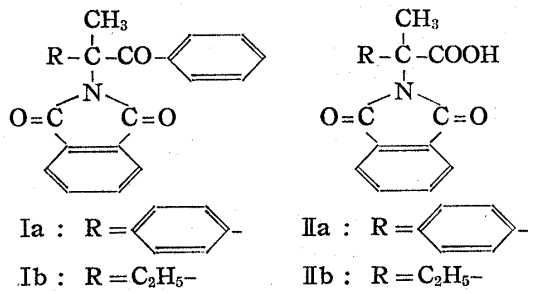
In an attempt to prepare α-methyl-α-phthalimidodeoxybenzoin (Ia) from N-phthaloyl-α-methylphenylglycine (IIa),[1] following to the same method as that used in the preparation of 2-methyl-2-phthalimidobutyrophenone (Ib) from N-phthaloylisovaline (IIb),[2] the acid chloride (III) prepared from IIa was refluxed with about an equimolar amount of anhydrous aluminum chloride in anhydrous benzene. From the reaction mixture, a neutral substance showing m.p. 103.5~105° was obtained as an only isolatable product. This compound gave a molecular formula, $C_{16}H_{11}O_2N$, being different from the expected formula $C_{23}H_{17}O_3N$. Its infrared spectrum in solid state showed the absorption at 1782, 1723 cm^{-1} due to N-phthaloyl group, 1635, 882 cm^{-1} indicating asymmetric disubstituted ethylenic group. The nuclear magnetic resonance spectrum*3 of this material showed multiplet at 2.36 τ (4 protons), three singlets at 2.81 τ (5 protons), 4.18 τ (1 proton) and 4.69 τ (1 proton). The signal of multiplet may be due to N-phthaloyl benzene ring protons and singlet at 2.81 τ to monosubstituted benzene ring protons. The singlets at 4.18 τ and 4.69 τ are probably ascribed to the two protons of the non-equivalent terminal asymmetric ethylenic group.



From the results described above, the material thus obtained was thought to be α-phthalimidostyrene (IV).

For the purpose of the further confirmation of the structure (IV), this compound (IV) was hydrogenated with Palladium-carbon in ethanol, followed by hydrolysis of N-phthaloyl group with acetic acid and conc. hydrochloric acid to give α-phenethylamine which was subsequently benzoylated with pyridine-benzoyl chloride to N-benzoyl-α-phenethylamine (V). This compound (V) showed the identical melting point with that already reported,[3] and in addition, V was synthesized by the alternative method.

Two isomers of α-methyldeoxybenzoin oxime, m.p. 122~125° and 109.5~110.5°, were obtained by fractional crystallization of crude oxime obtained from α-methyldeoxybenzoin[4] and hydroxylamine. The former has already been reported,[4] however the latter hitherto unreported. When both oximes were submitted to the Beckmann rearrangement respectively with phosphorus pentachloride in diethyl ether,[5] the latter oxime gave hydratropanilide (VII) and the former gave the compound which was identified on the mixed melting point and the infrared spectrum of which was superimposable

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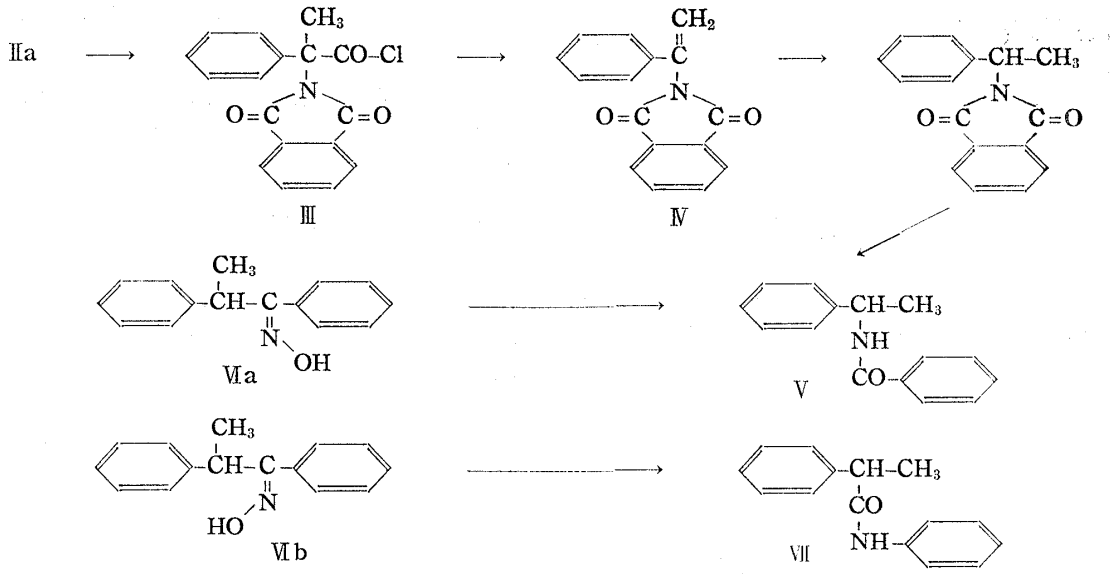
*3 The datum was observed in CCl_4, 60 Mc., TMS as internal standard.

1) S. D. Uphan, O. C. Dermer: J. Org. Chem., **22**, 799 (1957).
2) P. Freytag: Ber., **48**, 648 (1915).
3) M. Mètayer: Ann. chim., [12], **4**, 196 (1949).
4) V. Meyer, L. Oelkers: Ber., **21**, 1295 (1888).
5) G. Donarma, W. Z. Heldt: Org. Reac., **11**, 1 (1960).



with that of V.*4 From these results the structure of V has been clearly confirmed as N-benzoyl-α-phenethylamine, accordingly the structure of IV has also been proved, and at the same time it has been demonstrated that one oxime isomer (VIa), m.p. 122~125° has OH group *anti*, and another (VIb), m.p. 109.5~110.5°, *syn* to α-methyl-benzyl group.

The mechanism of this abnormal decarbonylation is not clear in detail. Even though the evolution of carbon monoxide was not detected, it might be deduced that the reaction proceeded under the sequence shown in Chart 1, and the reason why the acid chloride (III) undergoes such an abnormal decarbonylation is considered to depend on either the supposition that such a reaction is sterically more favorable than the normal Friedel-Crafts condensation, or that the carbonium ion (VIII) is stabilized by the resonance with benzene ring.

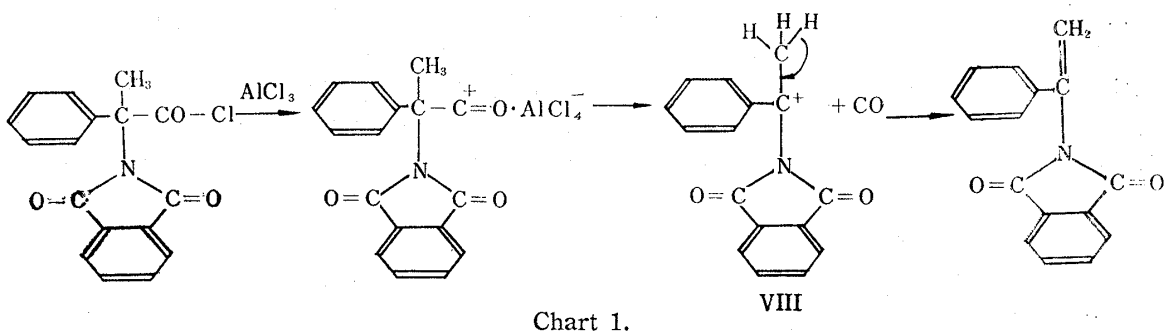


Chart 1.

Experimental*5

α-Phthalimidostyrene (IV) from N-Phthaloyl-α-methylphenylglycine(IIa)——A mixture of N-phthaloyl-α-methylphenylglycine (5.0 g., 0.017 mole) and PCl_5 (4.2 g., 0.020 mole) was heated at 80~90° on a water bath under slightly reduced pressure and shaken by hand occasionally. After 50 min. reflux, the resulting

*4 There are several examples in which two isomers of oximes are separated by fractional crystallization. For example, Kissmann, *et al.* obtained the two isomeric isobutyrophenone oximes by means of the slow crystallization from pentane, whose structures were determined by the Beckmann rearrangement using benzene-sulfonyl chloride and pyridine. (H. M. Kissmann, J. Williams : J. Am. Chem. Soc., **72**, 5323 (1950).)

*5 All the melting points were not corrected.

clear yellow solution was evaporated to dryness *in vacuo* to afford yellowish caramel (5.8 g.), to which was added anhyd. benzene (50 ml.) to dissolve. The lemon yellow benzene solution was decanted off from the undissolved material. To anhyd. $AlCl_3$ (2.3 g., 0.017 mole) was added this benzene solution and the mixture was refluxed on an oil bath for 45 min. under stirring. The gas evolution began at about 50°. The resulted brown colored solution was poured onto a mixture of ice (100 g.) and conc. HCl (100 ml.). The reaction vessel was washed with ether (60 ml.) and the ether washings were added to the benzene layer. The combined organic solvent layer was separated and washed successively with satd. NaCl solution, 10% Na_2CO_3 solution and then satd. NaCl solution. After dried over Na_2SO_4, the benzene solution was evaporated *in vacuo* to afford brownish white solid (3.8 g.) which was purified by column chromatography on silicic acid (20 g.) and the first fractions eluted with $CHCl_3$ gave crude Ⅳ after evaporation, m.p. 99~101.5° (3.5 g., 83%). Several recrystallization from CH_3OH gave white plates, m.p. 103.5~105°. *Anal.* Calcd. for $C_{16}H_{11}O_2N$: C, 77.09; H, 4.45; N, 5.62. Found : C, 77.31; H, 4.61; N, 5.57. IR ν_{max}^{KBr} cm^{-1} : 1782, 1723 (N-phthaloyl >C=O), 1635, 882 (>C=CH). NMR : τ value (solvent CCl_4, 60 Mc., TMS internal standard) : 4.69, singlet (1 proton); 4.18, singlet (1 proton); 2.81, singlet (1 proton); 2.36, multiplet (4 protons).

Separation of *syn*- and *anti*-Isomers of α-Methyldeoxybenzoin Oxime——To a solution of $NH_2OH \cdot HCl$ (4.0 g., 0.058 mole) and anhyd. CH_3COONa (4.8 g., 0.059 mole) in H_2O (20 ml.) was added a solution of α-methyldeoxybenzoin (10.0 g., 0.048 mole)[4] dissolved in EtOH (60 ml.). The reaction mixture was refluxed on a water bath for 4 hr., allowed to stand overnight, and eveporated to dryness to give a solid, from which organic substances were extracted with ether. After dried over Na_2SO_4, ether was evaporated to afford a white solid (10.5 g., crude yield 98.1%), m.p. 87.5~89°, clearly fused at 114°. This substance was dissolved in ether (40 ml.), and hexane (80 ml.) was added to this ethereal solution, the mixture was allowed to stand at room temperature to yield needles (6.0 g.), m.p. 113~120°, which were purified once with ether and hexane to give *anti*-isomer of α-methyldeoxybenzoin oxime (4.34 g., 40.5%), m.p. 123.5~127°. Several recrystallization from ether and hexane gave needles, m.p. 122~125°.[6] *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found : C, 80.18; H, 6.84; N, 6.57. IR ν_{max}^{KBr} cm^{-1} : 3300 (OH), 1600 (benzene), 762, 701 (monosubstituted benzene). Mother liquor from the first precipitation of *anti*-isomer was concentrated to about one-third of its initial volume and allowed to stand for 2 days at room temperautre to crystallize out needles (3.22 g.), m.p. 94~100°. Recrystallization from ether (8 ml.) and hexane (8 ml.) gave *syn*-isomer of the oxime as needles (1.36 g., 12.7%), m.p. 102~104°. Further recrystallization twice from the same solvents afforded needles m.p. 109.5~110.5°. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found : C, 79.81; H, 6.83; N, 6.12. IR ν_{max}^{KBr} cm^{-1} : 3270 (OH), 1598 (benzene), 762, 698 (monosubstituted benzene). IR spectra of the two isomers were different in solid state and in chloroform solution.

The Beckmann Rearrangement of *anti*-Isomer of α-Methyldeoxybenzoin Oxime——*Anti*-isomer (0.50 g., 0.002 mole) of α-methyldeoxybenzoin oxime was added to anhyd. ether (20 ml.) which was stirred and cooled. To this solution was added PCl_5 (0.50 g., 0.002 mole) all at once at a temperature of 0~5°. The reaction mixture was stirred for 1 hr. at this temperature, and then for additional 1 hr. at room temperature. H_2O (20 ml.) was added to the reaction mixture and agitation was continued for another 30 min. The upper ethereal layer was separated and washed with satd. NaCl solution, satd. $NaHCO_3$ solution and again satd. NaCl solution successively. After dried over Na_2SO_4, the ether solution was evaporated to dryness to afford N-benzoyl-α-phenethylamine (0.35 g., 70%) as a white solid,m.p. 118.5~119.5°. Recrystallization from benzene and hexane gave pure N-benzoyl-α-phenethylamine as white long needles, m.p. 123~123.5° (lit.[3]; m.p. 122°). IR ν_{max}^{KBr} cm^{-1} : 3375 (amide NH), 1631 (amide >C=O), 1604 (benzene), 1519 (amide Ⅱ).

The Beckmann Rearrangement of *syn*-Isomer of α-Methyldeoxybenzoin Oxime——*Syn*-isomer of α-methyldeoxybenzoin oxime (0.25 g,, 0.001 mole) was reacted with PCl_5 (0.25 g., 0.001 mole) in anhyd. ether (10 ml.) and treated similarly as mentioned above to yield yellowish white amide. Recrystallization from benzene and hexane gave hydratropanilide, white small needles (0.18 g.,72 %) m.p. 134.5~135° (lit.[7]; m.p. 134~135°). IR ν_{max}^{KBr} cm^{-1} : 3300 (amide NH), 1666 (amide >C=O), 1599 (benzene), 1548 (amide Ⅱ).

N-Benzoyl-α-phenethylamine (V) from α-Phthalimidostyrene (IV)——α-Phthalimidostyrene (Ⅳ) (1.0 g., 0.004 mole) was reduced in EtOH (40 ml.) over PtO_2 (0.10 g.) under H_2 atmosphere in ordinary pressure at room temperature. In 80 min., H_2 (99.7 ml.) was taken up (theoretical amount, 89.9 ml.). After filtration, EtOH was evaporated to give an oil (0.96 g.), which was solidified on standing, m.p. 69~110°. The hydrogenation seemed to be imcomplete,[8] so the further hydrogenation was carried out over 10% Pd-carbon (0.50 g.) in EtOH (60 ml.) containing conc. HCl (2 drops). After being treated as usual, a pale yellow oil (1.0 g.) was obtained which was chromatographed in $CHCl_3$ on silicic acid (50 g.) to give a yellow oil (0.67 g.).

6) This melting point is in accordance with that already reported : V. Meyer, L. Oelkers : Ber., **21**, 1295 (1888). m.p. 120°.
7) P. Arthur, Jr., D. C. England, B. C. Pratt, G. M. Whitman : J. Am. Chem. Soc., **76**, 5364 (1954).
8) The IR spectrum of this material was very similar to that of the starting material. The thin-layer chromatography also showed that this sample largely consisted of the starting material.

This oil was refluxed in a mixture of acetic acid (10 ml.) and conc. HCl (10 ml.) for 6 hr. After the evaporation of the solvents under reduced pressure, H_2O was added to the residue and an aqueous solution was made alkaline with NaOH pellets and extracted with ether. The ether extract was washed with satd. NaCl solution and then dried over anhyd. K_2CO_3. The evaporation of ether under N_2 atmosphere gave yellow oil (0.2 g.) which was treated with pyridine (2 ml.) and benzoyl chloride (8 drops). After kept standing overnight, the reaction mixture was poured onto ice and extracted with ether. The ether extract was washed successively with 10%HCl, satd. NaCl solution, satd. $NaHCO_3$ solution and satd. NaCl solution, dried over Na_2SO_4 and after removal of the solvent, yielded a pale yellow oil which solidified on standing for 2 days in dessicator. Recrystallization twice from benzene and hexane gave light pale yellow needles, m.p. 119~120.5°. A mixed melting point with N-benzoyl-α-phenethylamine (V) obtained from the Beckmann rearrangement showed no depression. The IR spectrum of this sample was essentially superimposable with that of V.

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Summary

When the chloride (Ⅲ) of N-phthaloyl-α-methylphenylglycine submitted to the Friedel-Crafts reaction, it was found that abnormal reaction occurred and α-phthalimidostyrene (Ⅳ) was obtained in good yield. Moreover, in the course of the demonstration of this structure, the structure of geometrical isomers of α-methyldeoxybenzoin oxime was established.

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133. Toshio Nambara and Mutsuji Yano*1 : Chemistry of C-16-Oxygenated 5α,14β-Androstanes.*2

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In the extension of our previous studies on conformation analysis of 14β-steroid, we wish to report the observations concerning metal hydride reduction of 16-oxo group and ring opening of 16β,17β-epoxide with hydrogen bromide.

The initial project was directed to reduction of 16-oxo-14β-steroid with use of metal hydride. 3β,17α-Dihydroxy-5α,14β-androstan-16-one diacetate (Ⅱ), prepared from 14β-isoandrosterone acetate (Ⅰ) in several steps,[1,2] was submitted to reduction with lithium aluminum hydride in ether. Treatment under mild condition gave 5α,14β-androstane-3β,16α,17α-triol (Ⅲa) as the sole product, which in turn was converted to acetonide (Ⅳa), m.p. 178~180°, and further to its 3-acetate (Ⅳb), m.p. 149~151°. It is sufficiently substantiated that of four possible 16,17-ketols in 14β-series 17α-hydroxy-16-ketone is the

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*2 This paper constitutes Part Ⅵ of the series entitled "Analytical Chemical Studies on Steroids"; Part Ⅴ : This Bulletin, **13**, 838 (1965).

*3 Hongō-7-chōme, Bunkyo-ku, Tokyō (南原利夫, 谷野睦治).

1) T. Nambara, J. Fishman : J. Org. Chem., **27**, 2131 (1962).
2) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, C. R. Scholz : J. Am. Chem. Soc., **74**, 5506 (1952).