Notes

[Chem. Pharm. Bull. 22(8)1917—1918(1974)]

UDC 547.466.64.05

Separation of Phthalyl-L- and -DL-Glutamic Acid on Their Solubility Difference

Yoshio Matsumoto and Etsu Takano

Department of Chemistry, Faculty of Hygienic Science, Kitasato University[1]

(Received January 29, 1974)

Phthalylation of L-glutamic acid by fusion of the mixture of L-glutamic acid and phthalic anhydride is the simplest method of the phthalylation, but inapplicable to the preparation of phthalyl-L-glutamic acid (I) because it always brings about a partial racemization of the amino acid in the fusion.[2]

In the course of our investigations synthesizing esters such as cholestanyl esters of amino acids, the authors found that although both phthalyl-L-glutamic acids (I) and phthalyl-DL-glutamic acid (II) have low solubilities in water at low temperatures, the L-isomer (I) showed a rapid increase in the solubility with an elevation of temperature, while the DL-isomer did not show such an increase.

Taking advantage of their solubility difference in water at an elevated temperature, either the L- (I) or the DL-isomer (II) could be isolated from their mixture. The isolation of the L-isomer required several repeating extractions with hot water and crystallization of the extractants by cooling. The DL-isomer could be more easily isolated in a crystalline form by dissolving the mixture of the L- and the DL-isomer in warm dioxane, and then by adding warm water gradually to the solution.

Fig. 1 shows the solubilities of the L- (I) and the DL-isomer (II) in water at various temperatures from 5 to 80°.

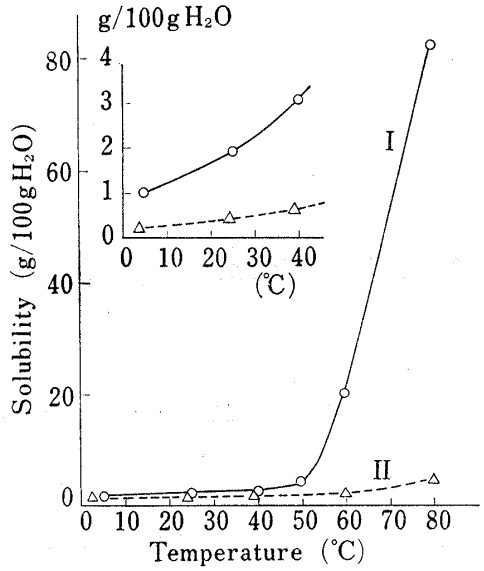

Fig. 1. Solubilities of Phthalyl-L-glutamic Acid (I) and Phthalyl-DL-glutamic Acid (II) in Water

—○—: phthalyl-L-glutamic acid (I)
---△---: phthalyl-DL-glutamic acid (II)

Experimental

Phthalyl-L-glutamic Acid (I)——An equimolecular mixture of L-glutamic acid (25 g, 0.17 mole) and phthalic anhydride (25 g, 0.17 mole) was heated at 140—150° for about 90 minutes until complete dissolution was observed. The reaction mixture was extracted with hot water (80°, 30 ml) adequate to dissolve all the phthalyl-L-glutamic acid (I) and to allow the DL-isomer (II) and the remaining reactants dissolved only scantly.

In order to precipitate the L-isomer alone, the extract was cooled to 30° after being diluted with 270 ml of hot water (80°). Twenty grams of crystals, $[\alpha]_D^{22}$ −41°, was obtained. Four times recrystallizations at 70° including once treatment with Norit A (1 g) gave 9 g of crystals, $[\alpha]_D^{22}$ −49.6° (c=3, dioxane),[3] mp

1) Location: *1, Asamizodai, Sagamihara, Kanagawa.*
2) F.E. King and D.A.A. Kidd, *Nature*, **162**, 776 (1948).
3) Measured by using a Yanagimoto automatic polarimeter OR-50.

160—161°. These values agreed with those in the literature[4-6] and also with those of the isomer synthesized through the Nefkens' method.[6] The yield was 20% of the theoretical. Optical purity of this phthalyl-L-glutamic acid (I) was confirmed by the fact that the hydrolyzing solution of the end-product, cholestanyl hydrogen-L-glutamate, with 6N HCl gives a value of $[\alpha]_D^{22}$ +23.6° (c=6, H_2O), which is identical to that of L-glutamic acid hydrochloride.

Phthalyl-DL-glutamic Acid (II)——A mixture (2.34 g, $[\alpha]_D^{22}$ −15.28°, c=3, dioxane) of the phthalyl-L-glutamic acid (I) and the DL-isomer (II) was dissolved in dioxane (60 ml) at 60° and to the resulting solution was gradually added 4 times its volume of water (60°) with stirring. The solution was kept at the same temperature for 2 hr to precipitate white crystals. By repeating this procedure, 0.9 g of crystals ($[\alpha]_D^{22}$ 0°, c=3, dioxane; mp 190—193°) was obtained. These values agreed with those of the DL-isomer (II) being prepared by a known method[7] *via* DL-α-pyrrolidonecarboxylic acid from the L-glutamic acid.

Acknowledgement The authors are grateful to Dr. Konomu Matsumura for his aids and advices, and also to Dr. Yukichi Yoshino, the professor of the University of Tokyo, for kindly allowing us to use an automatic polarimeter in his laboratory. We thank to Miss Kumiko Tsuji and Mr. Toshitaka Tamura for preliminary contribution to this work.

4) R.S. Tipson, *J. Org. Chem.*, **21**, 1353 (1956).
5) J.W. Clark-Lewis and J.S. Fruton, *J. Biol. Chem.*, **207**, 477 (1954).
6) G.H.L. Nefkens, G.I. Tesser, and R.J.F. Niverd, *Rec. Trav. Chim.*, **79**, 688 (1960).
7) M.S. Dunn and M.P. Stoddard, *Biol. Chem. Prep.*, **2**, 69 (1952).

[Chem. Pharm. Bull. 22(8)1918—1920(1974)]

UDC 547.743.1.057 : 543.422.8.615.06

Radiation Protective Agents. VI.[1] Synthesis of L-2-Pyrrolidinylmethyl Derivatives

KATSUKO UOJI, SHIRO IKEGAMI, and SANYA AKABOSHI

Division of Pharmaceutical Chemistry, National Institute of Radiological Sciences[2]

(Received January 30, 1974)

The radiation protective effects of various organic chemicals have been extensively investigated[3-6] and it has been generally recognized that mercaptoethlamine (MEA) and its isothiuronium salt (AET) are the most effective to the radioprotection. Based on this fact, we have examined the syntheses[7] and the radioprotective effects[8] of compounds related to AET.

1) Part V: T. Hino, K. Tsuneoka, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **18**, 389 (1970).
2) Location: *4-9-1, Anagawa, Chiba-shi, 280, Japan.*
3) *a*) H.M. Patt, E.B. Tyree, R.L. Straube, and D.E. Smith, *Science*, **110**, 213 (1949); *b*) *Idem, Proc. Soc. Biol. Med.*, **73**, 198 (1950); **80**, 92 (1952).
4) *a*) Z.M. Bacq, *Acta Radiologica*, **41**, 47 (1954); *b*) *Idem, Strahlentherapie*, **95**, 215 (1954).
5) *a*) H. Langendorff, *Strahlentherapie*, **93**, 281 (1954); *b*) H. Langendorff and R. Koch, *Strahlentherapie*, **94**, 411 (1954); **95**, 535 (1954); **98**, 245 (1955); **99**, 567 (1956); *c*) H. Langendorff, R. Koch, and U. Hagen, *Strahlentherapie*, **95**, 238 (1954); **100**, 137 (1956).
6) *a*) D.G. Doherty and W.T. Burnett, *Proc. Soc. Exp. Biol. Med.*, **89**, 312 (1955); *b*) D.G. Doherty, W.R. Burnett, and R. Shapira, *Radiation Research*, **7**, 1322 (1957).
7) *a*) T. Hino, K. Tanaami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1193 (1966); **14**, 1201 (1966); *b*) K. Uoji, K. Tsuneoka, A. Hanaki, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1742 (1969).
8) *a*) Y. Takagi, F. Sato, M. Shikita, M. Shinoda, T. Terashima, and S. Akaboshi, *Radiation Research*, **42**, 79 (1970); *b*) M. Shinoda, S. Shimizu, T. Hino, B. Tamaoki, and S. Akaboshi, *Yakugaku Zasshi*, **92**, 442 (1972).