SYNTHESIS OF THE R-FORM OF α-PHOSPHATIDYL-α-ALANYLGLYCERIN AND INVESTIGATION OF THE CONFIGURATION OF BACTERIAL LIPOAMINO ACIDS

Yul. G. Molotkovskii
and L. D. Bergel'son

UDC 542.91+535.56+547.466.547.915.5

In our previous communication [1] we described the synthesis of optically active lipoamino acids – R-3-(1',2'-distearoylglycerylphosphoryl)-1-L-alanylglycerin* (I) and its S-isomer. However, the method used for the production of (I) did not give satisfactory results, since it proceeded only with a negligible total yield.

In this work we are reporting on the synthesis of the R-isomer of (I) according to a new scheme, which can be used as the basis of a general method of producing compounds of this type. D-1,2-O-isopropylideneglycerin (II), when treated with triphenylchloromethane in pyridine, formed r-1,2-O-isopropylidine-3-O-tritylglycerin (III), m.p. 89-90° (hexane), $[\alpha]_D^{20}$ 15.5° (C 8.4; dioxane). After hydrolysis of (III) with trichloroacetic acid in aqueous dioxane at room temperature for three to four days, R-3-O-tritylglycerin (IV), m.p. 95-96° ($CHCl_3$ – hexane), $[\alpha]_D^{20}$ +9.55° (C 5.6; dioxane) was isolated from the reaction products by chromatography on aluminum oxide. Esterification of the product with N-carbobenzoxy-L-alanine in the presence of dicyclohexylcarbodiimide led to S-1-(carbobenzoxy-L-alanyl)-3-O-tritylglycerin (V), m.p. 120-121° (ether–petroleum ether), $[\alpha]_D^{19}$ -5.05° (C 6.9; dioxane), which, upon benzylation with benzyl bromide in the presence of Ag_2O, gave S-1-(N-carbenzoxy-L-alanyl)-2-O-benzyl-3-O-tritylglycerin (VI) in the form of an oil with $[\alpha]_D^{19}$ -4.3° (C 5; dioxane). Splitting out of the trityl group from (VI) was conducted on active silica gel under conditions not accompanied by acyl migration [3, 4]. The oily S-1-(N-carbobenzoxy-L-alanyl)-2-O-benzylglycerin (VII) obtained, $[\alpha]_D^{20}$ – 8.3° (C 7.1; dioxane), was treated with p-toluenesulfonyl chloride in pyridine, while the unpurified tosylate formed (VIII) was converted by the action of NaI in acetone to the R-1-(N-carbobenzoxy-L-alanyl)-2-O-benzyl-3-iodohydrin of glycerin (IX), m.p. 78.5-80° (ether–petroleum ether), $[\alpha]_D^{20}$ – 11.0° (C 7.3; dioxane) (see scheme on following page).

The iodide (IX) was also synthesized in another way: S-1-O-trityl-2-O-benzylglycerin (XI) [1] was converted through the tosylate (XII) to the oily R-iodohydrin (XIII), $[\alpha]_D^{20}$ – 8.8° (C 5.6; dioxane). The latter was hydrolyzed with dilute H_2SO_4 in aqueous dioxane, and the R-2-O-benzyl-3-iodohydrin of glycerin (XIV) formed (oil), $[\alpha]_D^{20}$ +4.9° (C 7; dioxane), was esterified with N-carbobenzoxy-L-alanine in the presence of dicyclohexylcarbodiimide to (IX).

The condensation of (IX) with silver 1,2-distearoylglycerylbenzylphosphate (X) (produced just like the analogous racemate [5]), led to the triphosphate (XV), a waxy substance with m.p. 36-38° (acetone), $[\alpha]_D^{19}$ + 0.3° (C 10; dioxane). The latter, after hydrogenolysis over $Pd/BaSO_4$ in dioxane, gave the lipoamino acid (I) sought, in the form of a colorless powder, which softens at ~ 80°, melts partially at 95-100°, and melts entirely at 175-178°, $[\alpha]_D^{20}$ +2.9° (C 2.1; $CHCl_3$). Found %: P 3.68; N 1.41. $C_{45}H_{88}O_{11}NP$. Calculated %: P 3.65; N 1.65. From its chromatographic behavior and its IR spectrum, the lipoamino acid (I) proved entirely identical with the compound described in the communication [1]. In elementary analysis, both preparations gave lowered values for the carbon content.† We believe, however, that formula (I) corresponds to them, since their spectra coincide entirely with the spectrum of the corresponding S-epimer [1].

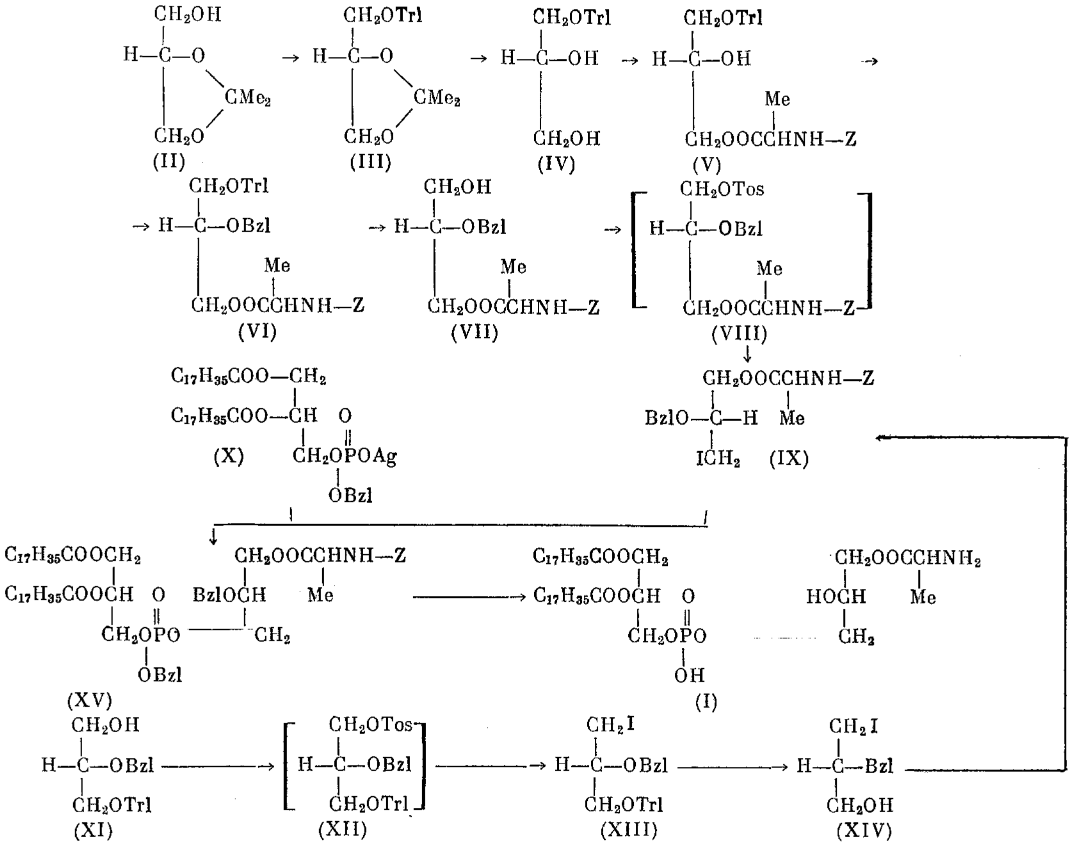
In its chromatographic behavior, the lipoamino acid (I) differs appreciably from the O-alanyl ester of phosphatidylglycerin ("fraction C"), isolated from Clostridium welchii [6]. At the same time, the R_f values of the natural product and the synthetic S-epimer of [1] practically coincide. Therefore it seems

---

* For the numeration of the C-atoms in optically active glycerides, see [2].

† For all the remaining substances described in this work, the data of elementary analysis corresponded to the calculated values.

Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 925-927, April, 1967. Original article submitted October 7, 1966.



Bzl = $C_6H_5CH_2$, Z = $C_6H_5CH_2OCO$, Trl = $(C_6H_5)_3C$, Tos = p-$CH_3C_6H_4SO_2$

probable that in the natural lipoamino acid, the glycerin residue bonded to alanine possesses an S-configuration. This conclusion agrees with the results obtained in [7] in an investigation of α-phosphatidyl-α-lysylglycerin, isolated from Staphylococcus aureus.

CONCLUSIONS

1. A new total synthesis of R-α-L-alanyl-γ-L-phosphatidylglycerin, optically active at all the asymmetric centers, was carried out.

2. A comparison of the synthetic preparation with the lipoamino acid from Clostridium welchii indicates that the latter is S-1-(L-phosphatidyl)-3-alanylglycerin.

LITERATURE CITED

1. Yul. G. Molotkovskii and L. D. Bergel'son, Izv. AN SSSR, Ser. Khim., 1966, 1098.
2. H. Hirschmann H., J. Biol. Chem., 235, 2762 (1960).
3. D. Buchnea and E. Baer, J. Lipid Res., 1, 405 (1960).
4. L. T. Dorofeeva, E. I. Kovshev, L. V. Volkova, and N. A. Preobrazhenskii, Zh. Obshch. Khimii, 33, 1883 (1963).
5. J. W. Gielkens, M. A. Hoefnagel, L. J. Stegerhoek, and P. E. Verkade, Recueil trav. chim., 77, 656 (1958).
6. M. G. Macfarlane, Nature, 196, 136 (1962).
7. U. M. T.Houtsmuller and L. L. M. van Deenen, Biochim. et biophys. acta., 106, 564 (1965).