ASYMMETRIC SYNTHESIS OF HETEROORGANIC ANALOGS OF NATURAL PRODUCTS.

6. (S)-α-AMINO-ω-PHOSPHONOCARBOXYLIC ACIDS

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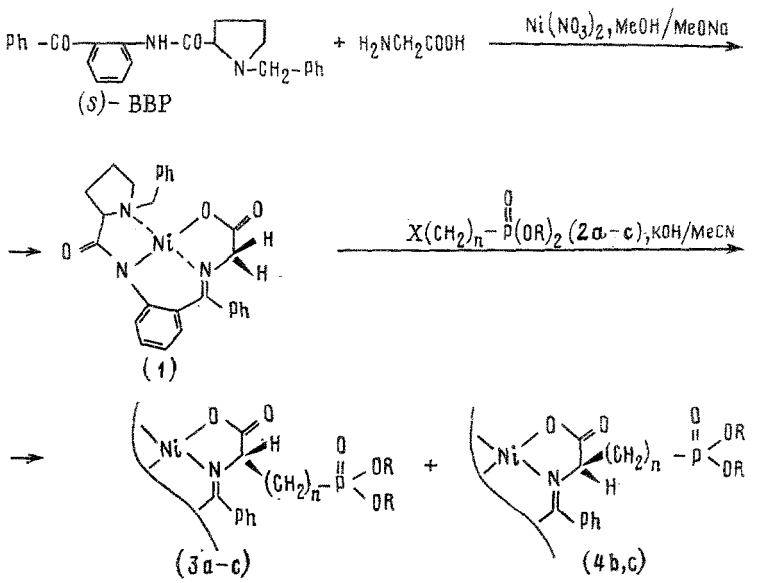
Alkylation, by ω-haloalkylphosphonates, of the Ni(II) complex of the Schiff base formed from glycine and (S)-2-N-(N[1]-benzylprolyl)-o-aminobenzophenone has been used for the asymmetric synthesis of (S)-2-amino-4-phosphonobutyric and (S)-2-amino-5-phosphonovaleric acids.

Keywords: asymmetric synthesis; (S)-α-amino-ω-phosphonocarboxylic acids.

The phosphorus analogs of amino acids, both natural and synthetic, have significant biological activity [1]. Of the analogs of dicarboxylic amino acids, phosphinothricin has attracted the most attention, together with the γ-methylphosphonic analog of glutamic acid, found in nature and having high antibacterial and herbicidal properties [2, 3], and α-amino-ω-phosphonocarboxylic acids. The latter compounds have been found to be effective and selective antagonists of amino acid generation (glutamate, N-methyl-D-aspartate (NMDA)) and have found wide use in the study of the mechanism of synaptic transmission [4-6], which has made it clear that the neuronal activity of these compounds is strongly dependent on their stereochemical structure. Thus, the (S)-isomer of 2-amino-4-phosphonobutyric is 20-40 times more active than the R-isomer in the suppression of glutamaturgic neurotransmission [7] and the activity of the strongest NMDA antagonist – 2-amino-5-phosphonovaleric acid – is shown mainly by the R-isomer [8, 9].

Scheme 1



X = I, Br; $n = 1$, R = Me_2CH (a); $n = 1$, R = Et (b); $n = 2$, R = Et (c).

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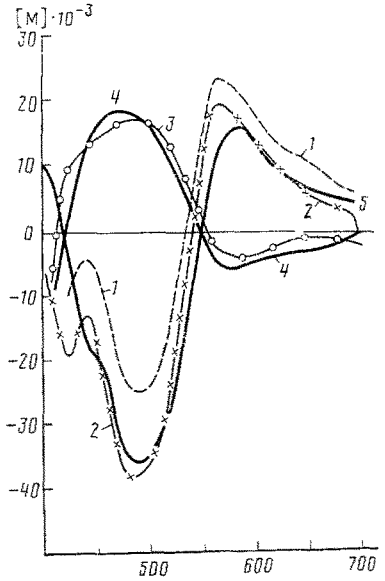


Fig. 1. ORD spectra of Ni(11) complexes of Schiff bases formed by(S)-2-N-(N^1-benzylprolyl) aminobenzophenone and esters of α-amino-ω-phosphonocarboxylic acids in $CHCl_3$ at 25°C: 1) (S)-2-amino-5-diethylphosphonovaleric acid; 2) (S)-2-amino-4-diethylphosphonobutyric acid; 3) (R)-2-amino-5-diethylphosphonovaleric acid; 4) (R)-2-amino-4-diethylphosphonobutyric acid; 5) (S)-2-amino-3-diisopropylphosphonopropionic acid.

It is thus of interest to search for convenient methods of preparing α-amino-ω-phosphonocarboxylic acids, particularly in enantiomerically pure form. Several methods have been developed for the synthesis of the phosphorus analogs of dicarboxylic acids [10, 11] and of these, methods employing a glycine synthon, either in alkylation by ω-haloalkylphosphonates [12-14] or in Michael addition reactions to vinyl phosphonates [15-17], seemed especially attractive in so far as these particular methods have been used in asymmetric syntheses of the compounds mentioned. Thus, both enantiomers of phosphonothricin were obtained by the method of Schollkopf [18], by alkylation of the chiral bis-lactim ester 2-chloroethylmethylphosphinate [19], and by Michael addition of a chiral Schiff base from glycine and (S)- or (R)-2-hydroxypinan-3-onespinan-3-ones to methylvinylphosphinate [20]. The use of a vinylphosphonate in a subsequent rection makes it possible to obtain (S)- and (R)-2-amino-4-phosphonobutyric acids [20].

This approach, however, does not completely solve the problem of preparing optically active α-amino-ω-phosphonocarboxylic acids and there is still a need to search for more general and practical alternatives.

We have previously developed general preparative methods for the asymmetrical synthesis of fluorine-containing phenylalanines [21], serines [22], and phenylserines [23] which involve alkylation by fluorine-containing alkyl halides and carbonyl compounds, of the readily accessible Ni(II) complex of the Schiff base prepared from glycine and (S)-N-(N^1-benzylprolyl)-o-aminobenzophenone (1) (scheme 1). In the present work, we have studied the alkylation of the complex 1 by ω-haloalkylphosphonates with the object of creating a convenient method for the asymmetrical synthesis of α-amino-ω-phosphonocarboxylic acids.

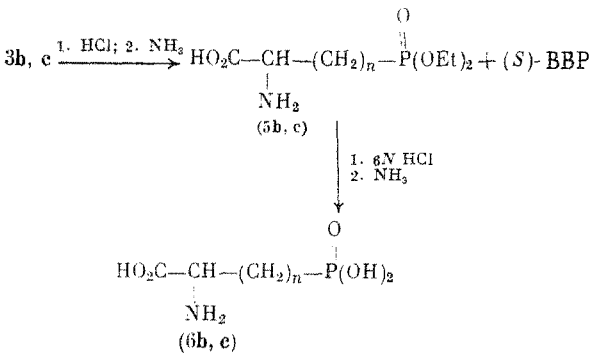
Alkylation of the complex 1 by phosphonated 2b, c was carried out in MeCN solution at 18-25°C in the presence of KOH and using a phase transfer catalyst, $\overset{+}{N}(Bu)_4Br^-$. The reaction resulted in a ~60% yield of a mixture of diastereomeric complexes 3b, c and 4b, c in 10:1 ratio respectively.

In contrast to 2b, c, reaction of 2a with complex 1 gave the desired product 3a in no more than 25-30% yield; this seems to be connected with the formation of several by-products which have proved difficult to identify. We separated the complexes 3a-c and 4b, c into their individual components by preparative chromatography on SiO_2. The composition and structure of compounds 3a-c and 4b, c were confirmed by elemental analysis and NMR spectroscopy.

The absolute configuration of the amino acids in complexes 3a-c and 4b, c was determined on the basis of their optical rotatory dispersion (ORD) spectra. It has been shown previously [24] that in the ORD spectra of Ni(II) complexes of (S)-α-amino acid Schiff bases, following the positive Cotton effects at 520-580 nm, there is a negative effect located at 410-500 nm, but for (R)-α-amino acids, on the other hand, the positive Cotton effects follow the negative. As can be seen from the results of the ORD spectra (Fig. 1), complexes 3a-c contain (S)-α-amino acid groups and complexes 4b, c the corresponding amino acid groups with (R)-α-configuration of the chiral carbon atom.

Isolation of the individual diastereo- and enantiomerically pure complexes 3b, c was carried out by the action of 2N HCl on a solution of the complexes in MeOH, separating the chiral inducing reagent (S)-BBP and the corresponding amino acids 5b, c (scheme 2).

Scheme 2



The amino acids 5b, c have not, apparently, been described in the literature, probably because of the complexity of their synthesis by general methods. Thus, in the majority of known methods for the preparation of α-amino-ω-phosphonocarboxylic acids the glycine synthon is used with protected carboxylate groups (esters) and the process of removing the protection also brings about the hydrolysis of the $P(O)(OR)_2$ group [11]. The milder conditions for the decomposition of the Ni(II) complex 3 make it possible to obtain the amino acids 5b, c as individual compounds in high yield. We obtained (S)-2-amino-4-diethylphosphonobutyric acid 5b in chemically and optically pure form and characterized it by elemental analysis and NMR spectroscopy.

An important difference between compounds 5 and the free α-amino-ω-phosphonoalkanoic acids 6 is the possibility of using ligand-exchange chromatography on chiral sorbents, described for general and fluorine-containing amino acids, for control of their enentiomeric purity [25]. Separation of the enantiomers of free α-amino-ω-phosphonocarboxylic acids 6 under these conditions has not up to now been successful.

Unsubtituted phosphorus analogs of the glutamic and homoglutamic acids 6b, c are prepared from the corresponding complexes 3b, c in two stages: via intermediate isolation of their esters 5b, c on a cation exchange resin and then, without further purification, hydrolysis to 6b, c. If the decomposition of the Ni(II) complexes 3b, c and hydrolysis of the esters 5 to amino acids 6 is carried out in one stage, incomplete removal of (S)-BBP as its hydrochloride results in the amino acids 6b, c being contaminated with hydrolysis products of (S)-BBP.

EXPERIMENTAL

NMR spectra were recorded on Bruker WP 200 (200 MHz) and Varian VXP 300 (300 MHz) intruments with internal standards HMDS (^1H) or H_3PO_4 (^{31}P). ORD spectra were run on a Jasko instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Enantiomeric analysis of the amino acids by ligand exchange chromatography was effected on an LKB instrument module with a column 250 × 4.0 mm packed with SI-100 Polyol Pro Cu 5 μm sorbent (Serva); the eluent was 5×10^{-3} M $CuSO_4$.

The chiral reagent (S)-BBP and the Ni(II) complex 1 were prepared by the method of [24]. MeCN was further purified by distillation over P_2O_5.

General Method for Alkylation of Complex 1 by ω-Halophosphonates 2a-c. To a solution of 10 mmoles complex 1 in 3 ml MeCN were added 13 mmoles of the corresponding ω-phosphonate, 50

mmoles of finely powdered KOH, and 0.5 g $Bu_4N^+Br^-$. The mixture was stirred in a current of Ar for 2 h at 20°C. It was then neutralized with 2N AcOH and extracted with $CHCl_3$, the extract dried over $MgSO_4$ and evaporated. The residue was chromatographed on SiO_2 ($L_{40}/_{100}$) in 5:1 $CHCL_3$–Me_2CO, separating the (S, R) diastereomers (4b) or (4c) (fraction 1), and (S, S) diastereomers (3a), (3b) or (3c) (fraction 2).

(S,S)-(3a), yield 30%, decomp. temp. 75-80°C, $[\alpha]_D^{25}$ + 1700 (c 0.5 $CHCl_3$). PMR spectrum (δ, ppm, J, Hz): 1.07 d (3H, CH_3, J = 7.5), 1.15 d (3H, CH_3, J = 7.4), 1.26 d (3H, CH_3, J = 7.5), 1.32 d (3H, CH_3, J = 7.5), 1.90-2.80 m (6H, Pro), 3.47 m (1H, α-H, Pro), 3.57, 4.46 (AB, 2H, CH_2-Bzl, J = 12.5), 3.65-3.86 m (2H, CH_2), 4.10 m (1H, α-H), 4.78 m (2H, 2CH), 6.63-8.35 m (14H, ArH). ^{31}P NMR spectrum ($CDCl_3$; δ, ppm): 24 m [P(O)(O-i-Pr)$_2$]. Found (%): C 60.45, H 5.95, N 5.99. Calculated for $C_{34}H_{40}N_3NiPO_6$ (%): C 57.32, H 5.66, N 5.90.

(S,S)-(3b), yield 64%, decomp. temp. 70-78°C, $[\alpha]_D^{26}$ + 2608 (c 0.5 $CHCl_3$). PMR spectrum ($CDCl_3$; δ, ppm, J, Hz): 1.27 t (3H, CH_3, J = 7.5), 1.28 t (3H, CH_3, J = 7.5), 1.60-2.80 m (8H, CH_2, Pro), 3.50-3.80 m (2H, CH_2), 3.45 m (1H, α-H, Pro), 3.55, 4.45 (AB, 2H, CH_2-Bzl, J = 12.5), 4.10 m (5H, $2CH_2$, α-H), 6.55-8.20 m (14H, ArH). Found (%): C 60.11, H 5.83, N 6.71. Calculated for $C_{33}H_{38}N_3NiO_6P$ (%): C 59.84, H 5.78, N 6.34.

(S,R)-(4b) yield 5%, decomp. temp. 88-93°C, $[\alpha]_D^{26}$ −873 (c 0.2, $CHCl_3$). PMR spectrum ($CDCl_3$; δ, ppm. J, Hz): 1.25 t (3H, CH_3, J = 7.5), 1.26 t (3H, CH_3, J = 7.5), 1.40-2.75 m (8H, CH_2, Pro), 3.60-3.75 m (2H, CH_2), 3.50 m (1H, α-H, Pro), 3.50, 4.43 (AB, 2H, CH_2–Bzl, J = 12.5), 4.15 m (5H, $2CH_2$, α-H), 6.60-8.50 m (14H, ArH). Found (%): C 60.09, H 6.10, N 6.51. Calculated for $C_{33}H_{38}N_3NiO_6P$ (%): C 59.84, H 5.78, N 6.34.

(S,S)-(3c), yield 57%, decomp. temp. 82-87°C, $[\alpha]_D^{28}$ +2282 (c 0.2, $CHCl_3$). PMR spectrum (CD_3COCD_3; δ ppm, J, Hz): 1.29 t (3H, CH_3, J = 7.8), 1.30 t (3H, CH_3, J = 7.7), 1.62-2.80 m (10H, $2CH_2$, Pro), 3.47 m (1H, α-H, Pro), 3.46-3.56 m (2H, CH_2), 3.56, 4.41 (AB, 2H, CH_2-Bzl, J = 12.5), 3.83 m (1H, α-H), 4.05 m (4H, $2CH_2$), 6.60-8.18 m (14H, ArH). ^{31}P NMR spectrum (CD_3COCD_3, δ, ppm): 30.34 m [P(O)(OEt)$_2$]. Found (%): C 60.21, H 6.03, N 6.34. Calculated for $C_{34}H_{40}N_3NiO_6P$ (%): C 60.37, H 5.96, N 6.21.

S,R-(4c): yield 4%, decomp. temp. 89-93°C, $[\alpha]_D^{28}$ −782 (c 0.3, $CHCl_3$). ^{31}P NMR spectrum (CD_3COCD_3; δ, ppm): 30.57 m [P(O)(OEt)$_2$]. Found (%): C 60.30, H 5.89, N 6.11. Calculated for $C_{34}H_{40}N_3NiO_6P$ (%): C 60.37, H 5.96, N 6.21.

(S)-2-Amino-4-diethylphosphonobutyric Acid (5b). A solution of 2 g complex (3b) in 7 ml MeOH was added to boiling 2N HCl and held until the color of the Ni complex (3b) had disappeared. The solution was evaporated, 10 ml H_2O added to the residue, the hydrochloride of (S)-BBP filtered off, and the aminoacid isolated from the aqueous layer by means of Dowex 50 cation exchange resin in H^+ form. Yield 69%, decomp. temp. 155-161°C, $[\alpha]_D^{25}$ +9.22 (c 0.5, H_2O). PMR spectrum (D_2O; δ, ppm, J, Hz): 1.53 t (6H, $2CH_3$, J = 7.0), 2.05-2.40 m (4H, $2CH_2$), 4.00 br. t (1H, α-H, J = 5.5), 4.35 m (4H, $2CH_2$). ^{31}P NMR spectrum (D_2O, δ, ppm): 33.99 m [P(O)(OEt)$_2$]. Found (%): C 38.84, H 7.59, N 5.69. Calculated for $C_8H_{18}NO_5P$ (%): C 40.16, H 7.58, N 5.86.

Isolation of (S)-BBP and Amino Acids from Complexes (3b, c). The complexes were decomposed by a method similar to the foregoing. The esters (5b, c) so obtained were hydrolyzed without further purification by boiling 6 h with 6N HCl. The free amino acids were isolated on Dowex 50 resin in H^+ form.

(S)-(6b), yield 64% decomp. temp. 227-232°C, $[\alpha]_D^{25}$ + 27.6 (c 0.3, 6N HCl). PMR spectrum (D_2O; δ, ppm, J, Hz): 1.7 m (2H, CH_2), 2.1 m (2H, CH_2), 4.0 br.t (1H, α-H, J = 6.1). ^{31}P NMR spectrum (D_2O; δ, ppm): 25.7 m [P(O)(OH)$_2$].

(S)-(6c), yield 51%, decomp. temp. 225-229°C, $[\alpha]_D^{25}$ +25.8 (c 0.1, 6N HCl). PMR spectrum (D_2O; δ, ppm, J, Hz): 1.5-2.3 m (6H, $3CH_2$), 4.1 br. t (1H, α-H, J = 6.1). ^{31}P NMR spectrum (D_2O, δ, ppm): 25.5 m [P(O)(OH)$_2$].

LITERATURE CITED

1. V. P. Kukhar', M. N. Solodenko, and V. A. Solodenko, Ukr. Biochem. Zh., 60, No. 6, 95 (1988).
2. E. Bayer, K. H. Gugel, K. Hagele, H. Hagenmaier, S. Jessipow, W. A. Konig, and H. Zaehner, Helv. Chim. Acta, 55, No. 1, 224-239 (1972).

3. W. Rupp, M. Finke, H. Bieringer, and P. Langelueddeke, W. Ger. Patent 2 717 440 (1977); Chem. Abs. 88, 70494 (1978).
4. S. G. Cull-Candy, J. F. Donnellan, R. W. James, and G. G. Lunt, Nature (London), 262, No. 5567, 408 (1976).
5. M. M. Slaughter and R. F. Miller, Science, 211, No. 4478, 182 (1981).
6. R. H. Evans, A. A. Francis, and K. Hunt, Br. J. Pharmacol., 67, No. 4, 591 (1979).
7. J. F. Koerner and C. W. Cotman, Brain Res., 216, No. 1, 192 (1981).
8. R. H. Evans, A. A. Francis, A. W. Jones, D. A. S. Smith, and J. C. Watkins, Br. J. Pharmacol., 75, No. 1, 65 (1982).
9. J. Davies, A. A. Francis, A. W. Jones, and J. C. Watkins, Neurosci. Lett., 21, No. 1, 77 (1981).
10. L. Maier, Phosphorus and Sulfur, 14, No. 3, 295 (1983).
11. V. P. Kukhar' and V. A. Solodenko, Usp. Khim., 56, No. 9, 1504 (1987).
12. P. Mastalerz, Acta Biochim. Polon., 4, No. 1, 19 (1957).
13. P. Mastalerz, Roczn. Chem., 33, Nos. 4-6, 985 (1959).
14. J. R. Chambers and A. F. Ishell, J. Org. Chem., 29, No. 4, 832 (1964).
15. H. Gross and T. Gnauk, J. Prakt. Chem., B318, No. 1, 157 (1976).
16. H. Gross and T. Gnauk, E. German Patent 116236 (1975).
17. N. Minowa, S. Fukatsu, T. Niida, M. Takada, and K. Sato, Tetrahedron Lett., 24, No. 23, 2391 (1983).
18. U. Schollkopf, Pure Appl. Chem., 55, 1799 (1983).
19. H.-J. Zeiss, Tetrahedron Lett., 28, No. 12, 1255 (1987).
20. H. Minowa, M. Hirayama, and S. Fukatsu, Tetrahedron Lett., 25, No. 11, 1147 (1984).
21. V. A. Soloshonok, Yu. N. Belokon', V. P. Kukhar', N. I. Chernoglazova, M. B. Saporovskaya, V. I. Bakhmutov, M. T. Kolycheva, and V. M. Belikov, Izv. Akad. Nauk, Ser. Khim., No. 7, 1630 (1990).
22. V. A. Soloshonok, V. P. Kukhar', A. S. Batsanov, M. A. Galakhov, Yu. N. Belokon', and Yu. T. Struchkov, Izv. Akad. Nauk, Ser. Khim., No. 7, 1548 (1991).
23. V. A. Soloshonok, V. P. Kukhar', S. V. Galushko, M. T. Kolycheva, A. B. Rozhenko, and Yu. N. Belokon', Izv. Akad. Nauk, Ser. Khim., No. 5, 1166 (1991).
24. Yu. N. Belokon', A. G. Bulichev, S. V. Vitt, Yu. T. Struchkow, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov, and V. M. Belikov, J. Am. Chem. Soc., 107, 4252 (1985).
25. S. V. Galushko, I. P. Shishkina, V. A. Soloshonok, and V. P. Kukhar', J. Chromatogr., 511, 115 (1990).