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ASYMMETRIC SYNTHESIS OF α-METHYLAMINOACIDS BY THE ALKYLATION OF GLYCINE, ALANINE, AND PHENYLALANINE IN CHIRAL Ni(II) COMPLEXES

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UDC 542.97:66.095.
253:547.466

α-Methylaminoacids display a wide spectrum of biological activity, and have found applications in medicine as therapeutic agents [1]. Furthermore, the incorporation of α-methylaminoacids into peptides greatly increases their stability to proteolytic enzymes [2]. α-Aminoacids (AA) of this type cannot be obtained microbiologically, and therefore the development of an efficient asymmetric synthesis of α-methyl-α-AA is of current interest. Several methods are known for the diastereoselective asymmetric synthesis of α-alkyl-α-AA in high chemical and optical yields [3-5]. The most interesting results have been obtained by alkylation of chiral bislactam diketopiperazines [3]. A drawback of this method is the number of stages involved, and the difficulty of separating the auxiliary chiral reagent from the reaction products.

We have previously reported the synthesis of α-methyl-α-AA by the alkylation of Ala in the Ni(II) complex of the Schiff's base with the chirally recoverable reagent S-2-N-(N'-benzylpropyl)aminobenzaldehyde [6]. However, the enantioselectivity of this reaction is poor, the enantiomeric purity of the S-α-methyl-α-AA obtained by this means being no greater than 40%.

We here report the asymmetric synthesis of α-methyl-α-AA by alkylating Ala, Phe, and Gly in the Ni(II) complexes of the Schiff's bases with S-2-N-(N'-benzylpropyl)aminobenzophenone (S-PAP). We assumed that the use of S-PAP, which contains a bulky phenyl substituent attached to the $\rangle C{=}O$ group, would to some extent increase the enantioselectivity of the reaction. In addition, it was of interest to examine the double alkylation of Gly in its chiral Ni(II) complexes.

Whereas Gly gives a single complex (III) with S-PAP, SR-α-AA give two diastereoisomeric complexes containing S-α-AA (SS-(I) and SS-(II)) and R-α-AA (SR-(I) and SR-(II)). The structure of (III) has already been proved by the authors [7], and those of complexes SS-(I), SR-(I), SS-(II), and SR-(II) are shown by their elemental analyses, PMR, CD, and electronic spectra (Table 1).

Complexes (I) and (II) are alkylated by alkyl halides in DMF in the presence of solid NaOH to give mixtures of SS- and SR-diastereoisomeric complexes (VI) and (VII), containing α-methyl-α-AA (Diagram 2).

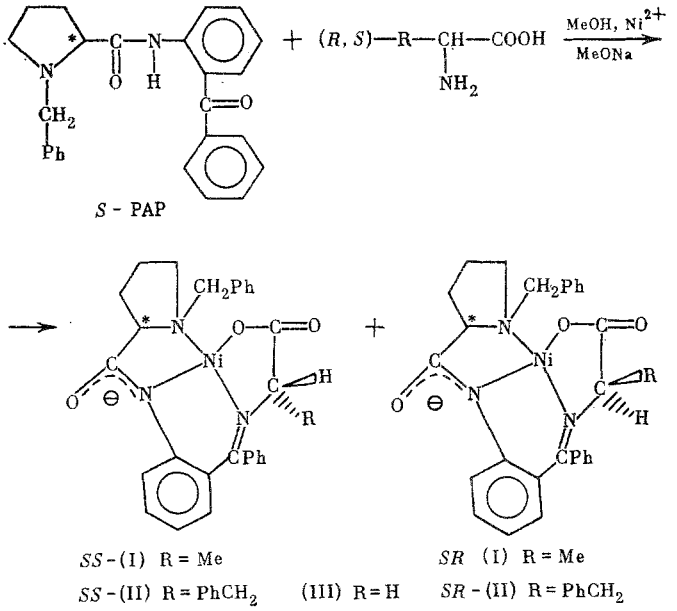
A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2798-2804, December, 1987. Original article submitted May 19, 1986.

0568-5230/87/3612-2595$12.50

TABLE 1. Composition of Complexes (S-PAP-AA)Ni(II)

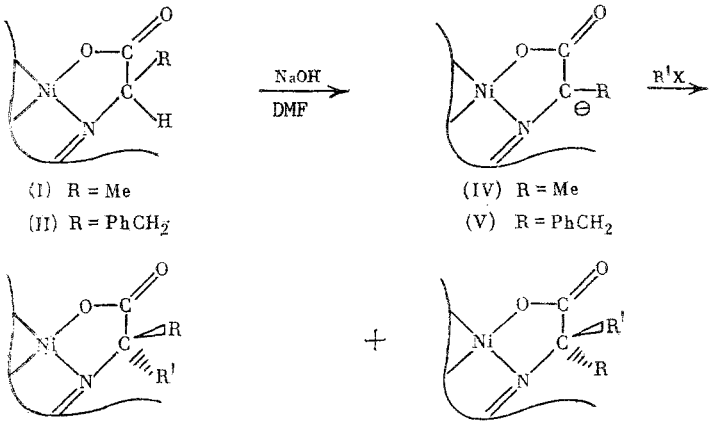
Compound	Empirical formula	Found/Calculated, %			Mp, °C	λ_{max} (lg ε), (MeOH)	$[M]_{\lambda}^{25}$ (MeOH)			
		C	H	N			578 nm	546 nm	436 nm	365 nm
SS-(I)	$C_{28}H_{27}N_3O_3Ni$	65,46 / 65,65	5,39 / 5,31	8,02 / 8,20	147–154	266(4,21) 332(3,62) 417(3,52) 531(2,27)	+17699	19734	−3097	−3982
SR-(I)	$C_{28}H_{27}N_3O_3Ni$	65,95 / 65,65	5,34 / 5,31	7,91 / 8,20	190–196	267(4,20) 332(3,69) 419(3,55) 540(2,20)	−2451	+4412	−12745	−4412
SS-(II)	$C_{34}H_{31}N_3O_3Ni$	69,61 / 69,41	5,44 / 5,31	7,53 / 7,13	241–246	265(4,32) 338(3,73) 420(3,54) 538(2,48)	+16393	+4918	−11855	+15164
SR-(II)	$C_{34}H_{31}N_3O_3Ni$	69,64 / 69,41	5,60 / 5,31	7,51 / 7,13	197–202	263(4,37) 335(3,91) 419(3,54) 533(2,21)	−1136	+3409	+7575	−4166
SS-(VI)	$C_{35}H_{33}N_3O_3Ni$	69,64 / 69,78	5,35 / 5,52	7,09 / 6,96	120–124	262(4,23) 335(3,68) 421(3,49) 524(2,37)	+16019	+6796	−9223	+5339
SR-(VI)	$C_{35}H_{33}N_3O_3Ni$	69,46 / 69,78	5,65 / 5,52	7,25 / 6,96	107–113	263(4,14) 331(3,65) 419(3,45) 521(2,18)	+13207	+11792	+6132	−29716
SS-(VII)	$C_{31}H_{31}N_3O_3Ni$	66,99 / 67,40	5,60 / 5,65	7,56 / 7,60	218–223	264(4,21) 332(3,74) 418(3,48) 531(2,27)	+14179	+9328	−1865	+9701
SR-(VII)	$C_{31}H_{31}N_3O_3Ni$	67,26 / 67,40	5,45 / 5,65	7,83 / 7,60	189–196	262(4,40) 330(3.60) 417(3,41) 521(2,12)	+11842	+9210	+3947	−16447

Diagram 1



SS-(I) R = Me
SS-(II) R = PhCH2 (III) R=H
SR (I) R = Me
SR-(II) R = PhCH2

Diagram 2



(I) R = Me
(II) R = PhCH2
(IV) R = Me
(V) R = PhCH2

SS-(VI) R = Me, R' = PhCH2,
SS-(VII) R = Me, R' = CH2CH=CH2
SR-(VI) R = PhCH2, R' = Me,
SR-(VII) R = Me, R' = CH2CH=CH2

The ratios of the SS- and SR-diastereoisomers (VI) and (VII) formed on alkylation are shown in Table 2. Complexes (VI) and (VII) may be obtained by double alkylation of Gly in complex (III), as shown in Diagram 3, the ratio of the resulting SS- and SR-diastereomers depending to a large extent on the order of addition of the alkylating agents (Table 2).

Alkylation of Ala in its complex (I) with allyl bromide or benzyl bromide, and double alkylation of Gly in (III) by method A (first MeI, then allyl bromide or benzyl bromide) in >80% excess gives the SS-diastereomers (VI) and (VII), containing S-α-methyl-α-AA (Table 2, Nos. 1, 2, 5, 6).

However, alkylation of Phe in complex (II) with MeI and double alkylation of Gly in (III) by method B (benzyl bromide or allyl bromide, followed by MeI) gave almost equal amounts of the SS- and SR-diastereomers (VI) and (VII) (Table 2, Nos. 3, 4, 7, 8).

Decomposition of the pure SS- and SR-diastereomers (VI) and (VII) with 2 N HCl gave 80-90% of the chiral inducing reagent S-PAP, recovered from the reaction mixture without loss of optical activity, and enantiomerically pure S- or R-α-methyl-α-AA. The absolute configurations of the α-methyl-α-AA obtained are readily found by using the vicinal contribution of the amino acid moiety in the CD spectra of the original diasteromeric

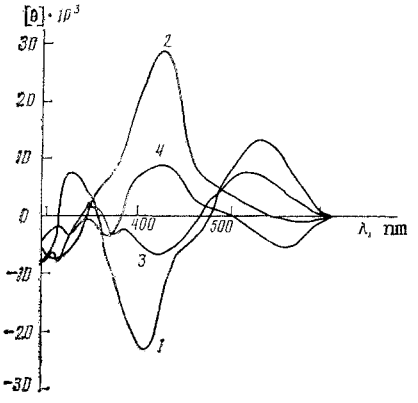


Fig. 1

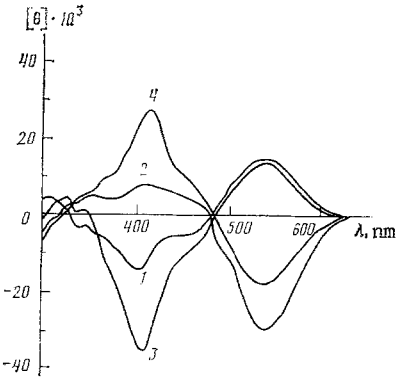


Fig. 2

Fig. 1. Vicinal contributions of aminoacid moieties in the CD spectra of Ni(II) complexes: 1) SS-(VI), 2) SR-(VI), 3) SS-(VII), 4) SR-(VII).

Fig. 2. Vicinal contributions of aminoacid moieties in the CD spectra of Ni(II) complexes: 1) SS-(I), 2) SR-(I), 3) SS-(II), 4) SR-(II).

TABLE 2. Chemical Yields and Diastereomer Ratios Obtained by Alkylation of Complexes (I)-(III)

Compound No.	Starting complex	RX	Diastereomer ratio, %		Overall chemical yield, %
			SS	*SR*	
1	*SS*-(I)+*SR*-(I)	$PhCH_2Br$	93	7	93
2	*SS*-(I)+*SR*-(I)	$CH_2=CHCH_2Br$	92	8	91
3	*SS*-(I)+*SR*-(I)	C^2H_3I	74	26	89
4	*SS*-(II)	MeI	48	52	92
5	*SR*-(II)	MeI	51	49	87
6	(III) *	MeI $CH_2=CHCH_2Br$	92	8	87
7	(III) *	MeI $PhCH_2Br$	91	9	84
8	(III) †	$PhCH_2Br$ MeI	51	49	91
9	(III) †	$CH_2=CHCH_2Br$ MeI	56	44	88

*Double alkylation of (III) was carried out by method A.
†Double alkylation of (III) was carried out by method B.

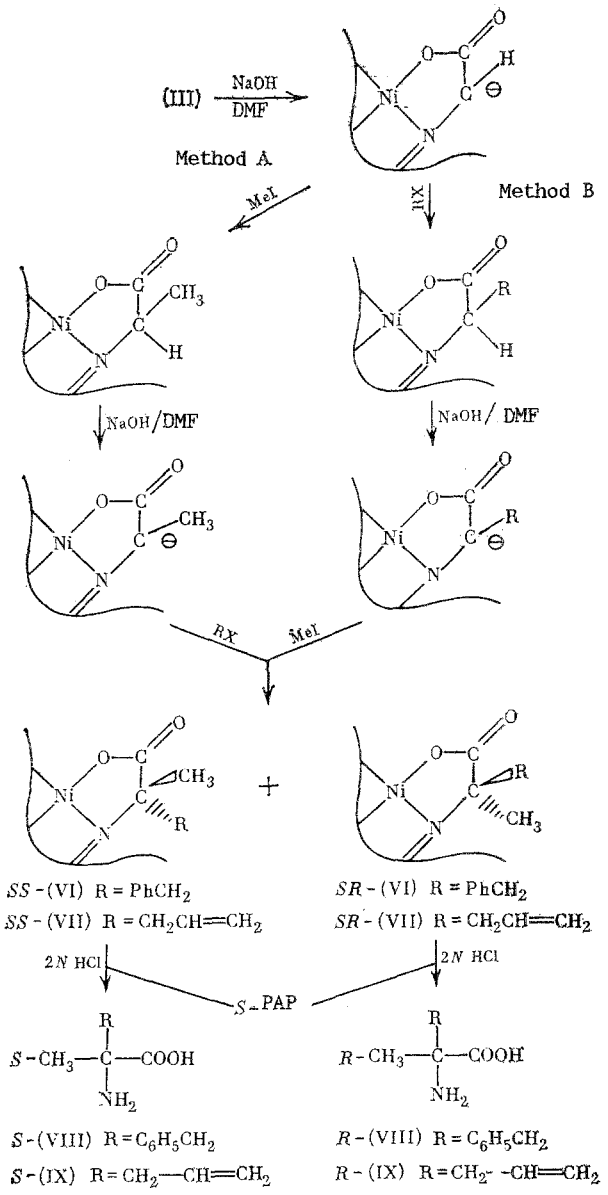
complexes [8]. Figure 1 shows the vicinal contributions of the S- and R-α-methyl-α-AA. For comparison, Fig. 2 shows the vicinal contributions of S- and R-Ala and S- and R-Phe in the CD spectra of (I) and (II), respectively. These values show that for amino acids with the S-configuration, the positive Cotton effects at 520-540 nm are followed by negative effects at 410-430 nm. With R-α-AA, on the other hand, the negative Cotton effects at 520-540 nm alternate with positive effects.

EXPERIMENTAL

'Reakhim' pure grade reagents were used, and the DMF was purified as described in [9].

PMR spectra were obtained on a Bruker WR-200 instrument (200 MHz), and electronic spectra on a Specord UV-VIS. CD spectra were recorded on a Jasko J-20. Optical rotations were measured on a Perkin-Elmer 241. The chiral reagent S-PAP and the complex (III) were obtained as described in [7].

Diagram 3



Complexes SS-(I) and SR-(I). To 1.5 g (3.9 mmoles) of S-PAP and 2.25 g (7.8 mmoles) of $Ni(NO_3)_2 \cdot 6H_2O$ in 23 ml of methanol was added a solution of 1.74 g (19.5 mmoles) of SR-Ala in 23 ml of 1.2 N MeONa. The mixture was stirred under argon for 2 h at 50°C, 75 ml of water added, extracted with chloroform (4 × 25 ml), the extracts evaporated, and the residue chromatographed on a column of SiO_2 L40/100μ in the system chloroform:acetone (5:1) to give the pure diastereomers SR-(I) (fraction 1) and SS-(I) (fraction 2). The SR- and SS-(I) were further purified on Sephadex LH-20 in the system benzene:ethanol (2:1), and dried in vacuo over P_2O_5 to give 0.127 g (6.3%) of SR-(I). PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.33 d (J = 7.5, 3H, CH_3), 1.91-4.19 m (7H, Pro), 3.85 q (1H, α-H, Ala), 6.62-8.45 m (14H, ArH), 3.38, 4.30 (AB, 2H, CH_2—benzyl, J = 12.5). Also obtained was 1.69 g (84.5%) of SS-(I). PMR spectrum (in $CDCl_3$, δ, ppm., J. Hz): 1.51 d (3H, CH, J = 7.5), 1.93-3.77 m (7H, Pro), 3.85 q (1H, α-H, Ala), 6.50-8.07 m (14H, ArH), 3.50, 4.38 (AB, 2H, CH_2—Benzyl, J = 12.5).

Complexes SR- and SS-(II). Obtained similarly, from 1.64 g (4.26 mmoles) of S-PAP and 3.54 g (21.3 mmoles) of S,R-Phe, was 0.102 g (4.2%) of SR-(II). PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.85-3.85 m (7H, Pro), 2.83, 2.97 (ABX, 2H, CH_2(Phe), J_{AB} = 14, J_{AX} = 6.2, J_{BX} = 5.8), 3.40, 3.68 (AB, 2H, CH_2—Benzyl, J = 12.5 Hz), 4.15 m (1H, α-H, (Phe)), 6.65-8.40 m (19H, ArH).

Also obtained was 2.1 g (88%) of SS-(II). PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.82-3.85 m (7H, Pro), 2.82, 3.07 (ABX) 2H, CH_2(Phe), J_{AB} = 14, J_{AX} = 6.0, J_{BX} = 6.2), 3.43, 4.25 (AB, 2H, CH_2-benzyl, J = 12.5), 4.25 m(1H, α-H, (Phe)), 6.63-8.20 m (19H, ArH).

General Method of Alkylation of Complexes (I) and (II) by Alkyl Halides. To a solution of 1 mmole of the complex in 3 ml of DMF was added 5 mmoles of the alkyl halide, 5 mmoles of finely-ground NaOH, and the mixture stirred for 2 h under argon at 20°C. It was then neutralized with 0.1 N HCl, 25 ml of water added, extracted with chloroform, and the extract evaporated. The residue was chromatographed on $L_{40}/100\mu$ silica in the system chloroform:acetone (5:1), to give the SS-diastereomers (VI) or (VII) (fraction 1) and the SR-diastereomers (VI) or (VII) (fraction 2). The yields of the complexes and the ratios of the diastereomers are given in Table 2.

SS-(VI), PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.11 s (3H, CH_3), 1.65-3.20 m (7H, Pro), 3.13 m (2H, CH_2—Phe), 3.48, 4.25 (AB, 2H, CH_2—benzyl, J = 12.5), 6.50-8.13 m (19H, ArH).

SR-(VI), PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.51 s (3H, CH_3), 1.93-3.70 m (7H, Pro), 2.82, 3.08 (AB, 2H, CH_2(Phe), J = 14.5), 3.35, 4.18 (AB, 2H, CH_2—benzyl, J = 12.5), 6.58-7.90 m (19H, ArH).

SS-(VII), PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.13 s (3H, CH_3), 1.87-3.51 m (7H, Pro), 2.43 d (2H, H_2C—), 3.65-4.43 (AB, 2H, CH_2—benzyl, J = 12.5), 5.35 m (2H, H_2C=, J_{trans} = 14, J_{cis} = 9, J_{gem} = 1), 6.63-8.19 m (14H, ArH).

SR-(VII), PMR spectrum (in $CDCl_3$, δ, ppm., J, Hz): 1.47 s (2H, CH_3), 1.93-3.76 m (7H, Pro), 2.18, 2.43 (ABX, 2H, H_2C—, J_{AB} = 14.5, J_{AX} = 7, J_{BX} = 6), 3.47, 4.38 (AB, 2H, CH_2—benzyl, J = 12.5), 5.21 m (2H, H_2C=, J_{trans} = 16, J_{cis} = 11, J_{gem} = 1), 5.75 m (1H, HC=), 6.45-8.13 m (14H, ArH).

General Method of Double Alkylation of (III). Method A. To a solution of 1 mmole of (III) in 3 ml of DMF was added 1 mmole of MeI, 5 mmoles of finely ground NaOH, and the mixture stirred under argon for 30 min. Allyl bromide or benzyl bromide (5 mmoles) was then added, and the mixture stirred for 2 h. The mixture was worked up and the pure diastereomers (VI) and (VII) isolated as described above.

Method B. To a solution of 1 mmole of (III) in 3 ml of DMF was added 1 mmole of benzyl bromide or allyl bromide and 5 mmoles of finely divided NaOH, and the mixture stirred for 2 h. It was then worked up and the pure diastereomers (VI) and (VII) isolated as described above. The yields of the complexes and the diastereomer ratios are given in Table 2.

Isolation of S-PAP and Aminoacids from Complexes SS-(VI), SR-(VI), SS-(VII), and SR-(VII). The complexes were decomposed by a general method. To 20 ml of a boiling 2 N solution of HCl was added dropwise a solution of 6 mmoles of the complex in the minimum amount of ethanol. When the color had disappeared (5-20 min), the solution was neutralized with 20% ammonia to pH 8-9, and the S-PAP extracted with chloroform. The yield of the reagent in the various experiments was 80-90%. The amino acids were extracted from the aqueous layer on Dowex-50 resin (H^+-form). The yields of the amino acids ranged from 70 to 80%.

S-α-Methyl-Phe(S-VIII): optical purity > 99%, decomp. 298-300°C (from ethanol), $[\alpha]_D^{25}$—4.51° (c 1.04, 1N HCl). Found, %: C 55.44, H 8.66, N 10.62. $C_6H_{11}NO_2$. Calculated, %: C 55.80, H 8.59, N 10.84. PMR spectrum (in D_2O, δ, ppm., J, Hz): 1.38 s (3H, CH_3), 2.78, 3.10 (AB, 2H, CH_2, J = 14), 7.13 m (5H, ArH).

R-α-Methyl-Phe(R-VIII): optical purity > 99%, $[\alpha]_D^{25}$ + 4.2° (c 1.01, 1 N HCl).

S-α-Allyl-Ala(S-IX): optical purity > 99%, decomp. 306-309°C (from ethanol), $[\alpha]_D^{25}$—14.4° (c 1.3, 1N HCl), $[\alpha]_D^{25}$—28.5° (c 1.3, H_2O). Found, %: C 55.44, H 8.66, N 10.62. $C_6H_{11}NO_2$. Calculated, %: C 55.80, H 8.59, N 10.84. PMR spectrum (in D_2O, δ, ppm., J, Hz): 1.30 s (3H, CH_3), 2.20, 2.48 (ABX, 2H, H_2C—, J_{AB} = 14, J_{AX} = 8.5, J_{BX} = 8), 5.07 m (2H, H_2C=), 5.55 m (1H, HC=).

Rα-Allyl-Ala(R-IX): optical purity > 99%, $[\alpha]_D^{25}$ + 14.2° (c 0.96, 1 N HCl).

CONCLUSIONS

Alkylation of alanine, phenylalanine, and glycine in the Ni(II) complexes of their Schiff's bases with S-2-N-(N'-benzylpropyl)aminobenzophenone followed by chromatographic separation of the diastereomers has given optically pure S- and R-α-methyl-α-aminoacids.

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STUDY OF HALOGENATION OF 3-HYDROXYMETHYLCYCLOHEXENE

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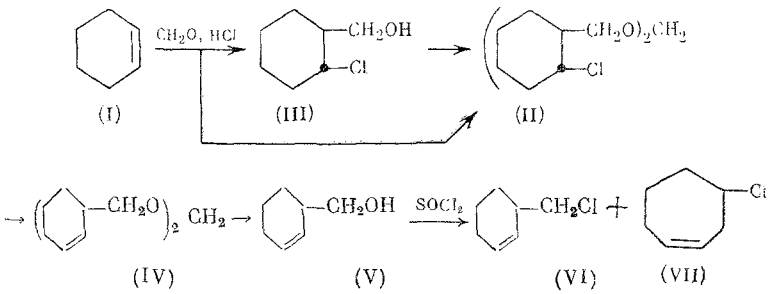
UDC 541.124.542.944: 547.593.3

The scheme of transformation of cyclohexene (I) into 3-chloro-methylcyclohexene (VI) that we have already proposed [1-4] gave a moderate yield (42%) of 3-hydroxymethylcyclohexene (V) and also led to a mixture (2:1) of chloride (VI) with 4-chlorocycloheptene (VII):



The present investigation has been undertaken to increase the yield of alcohol (V) and to clarify the reasons for its anomalous chlorination. Since alcohol (V) is obtained from formal (II), we varied the conditions of the reaction of cyclohexene, CH_2O and HCl, and showed that at 20°C only 62% of cyclohexene reacts after 3 h, while at 30°C, all (I) enters into the reaction in the course of 6 h. The methanolysis of formal (II) gives alcohol (III), which when treated with alcoholic alkali gives the reversed Prins reaction [5, 6]. Treatment with an aqueous—alcohol solution of AcOK leads to alcohol (V) (75%) and 1-hydroxymethyl-2-hydroxycyclohexanes (VIII) and (IX) (25%), identified in the form of cyclic formals (1,3-dioxadecalins) (X) and (XI)

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2805-2809, December, 1987. Original article submitted May 23, 1986.

0568-5230/87/3612-2601$12.50