SEMISYNTHETIC β-LACTAM ANTIBIOTICS. II[1]

CEPHALOSPORIN DERIVATIVES IN THE NAPHTHALENE SERIES CHEMICAL AND MICROBIOLOGICAL PROPERTIES

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A series of new 7-acylamidocephalosporins, containing a substituted naphthalene moiety in the side chain, has been prepared and tested for their *in vitro* antibacterial activity. Some observations are made on the structure-activity relationships.

β-Lactam antibiotics are known to interfere with the final stage of bacterial cell wall biosynthesis[2]. Structural changes of these antibiotics affect cell-wall permeability which appears to be mediated by compound polarity. Therefore, lipophilia and hydrophilia are very important parameters in assessing how a drug penetrates the bacterial cell wall[3]. Cephalosporins which are most active against Gram-positive microorganisms are more lipophilic than those which are active against Gram-negative microorganisms[4]. The low lipid content of the cell wall of Gram-positive microorganisms cannot retain the most lipophilic molecules, which are then able to reach their site of action. Therefore, the most lipophilic compounds cannot but have high activity against Gram-positive microorganisms. In the case of Gram-negative microorganisms, the high lipid content of their cell wall would not permit the activity of more lipophilic compounds. It has been shown that cephalosporins with aromatic fused rings in the side chains in position 7 have a marked activity against Gram-positive microorganisms and are inactive against Gram-negative microorganisms[5,6].

We have synthesized several variously substituted 7-naphthylacylamido cephalosporins in order to study the effect of the variation on antibacterial activity.

Chemistry

The new semisynthetic cephalosporins were synthesized by acylating 7-ACA or 7-ADCA, using two general methods, as outlined in Scheme 1. In particular, 7-acylamidocephalosporanic and desacetoxycephalosporanic acids (**II**) were prepared directly by acylation of 7-ACA or 7-ADCA (**I**) with some acid chlorides synthesized by literature procedures. This coupling reaction was carried out by a modified SCHOTTEN-BAUMMAN method using the sodium salt of 7-ACA or 7-ADCA in aqueous acetone (method "A"). The final cephalosporins were characterized as free acids or as their sodium salts. In addition, the derivatives (**IV**) were prepared from 7-ACA or 7-ADCA (**I**) through the intermediate bromo derivatives (**III**) ($R''=H$)[7,8], ($R''=CH_3$)[6] *via* nucleophilic displacement of the bromine atom by thiols and thiolcarboxylic acids. This reaction was carried out in aqueous acetone or dichloromethane; sodium bicarbonate or triethylamine were used, respectively, as acid acceptors (method

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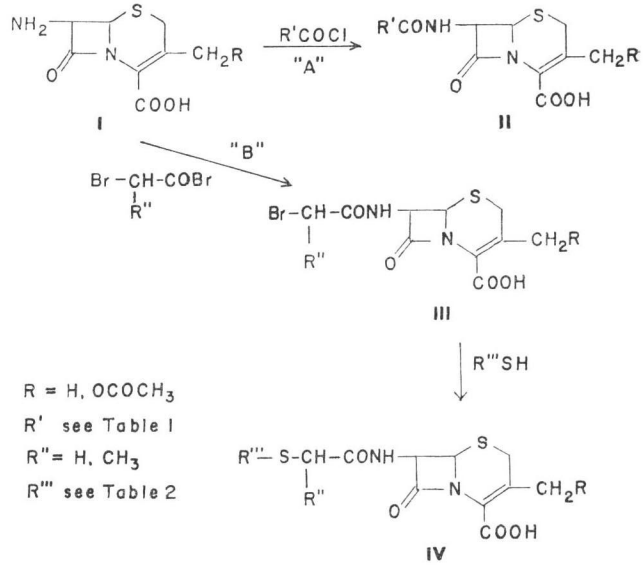
"B").

Derivatives with R′, R″ and R‴ are listed in Tables 1 and 2. These compounds where isolated in crystalline form and their structures were characterized by spectral and analytical data; the NMR spectra of each compounds were consistent with the proposed structures. The chemical shifts of the protons of the cephem moiety were in agreement with those described for 7-ADCA and 7-ACA[9] and are not reported in Table 1.

Scheme 1.



Antibacterial Properties

A fresh solution of the antibiotic for the *in vitro* test was prepared daily by dissolving it in a saturated sodium bicarbonate solution directly or after first dissolving it in N,N-dimethylformamide when the antibiotic was only slightly soluble in the former solution.

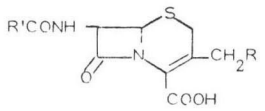
The bacterial strains employed were clinical isolates obtained from medical centres in Rome and identified by standard criteria (22 *Escherichia coli*, 10 *Salmonella* spp., 10 *Klebsiella* spp., 12 *Proteus mirabilis*, 10 *Pseudomonas aeruginosa*, 6 Enterococcus spp.) or strains taken from research laboratory cultures (19 penicillin-resistant and non-resistant *Staphylococcus aureus*).

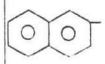
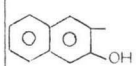
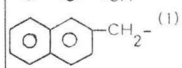
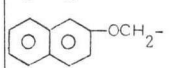
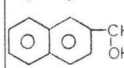
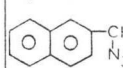
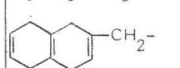
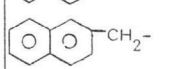
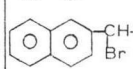
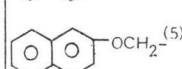
The minimum inhibitory concentrations (MIC'S) of the antibacterial agents were determined by the usual two-fold serial agar dilution technique. Test cultures grown in appropriate broth media for about 18 hours at 37°C were deposited on the solidified surface of the agar using a multiple inocula replicator designed to deposit a loop-ful containing approximately 10^6 CFU on the agar surface (Penassay seed agar, Difco). The plates were incubated aerobically at 37°C. The MIC was defined as the lowest concentration at which the visible growth of a test organism is completely inhibited.

The more interesting data are reported in Table 3. The results are expressed as the number of strains inhibited by more significant concentrations of new cephalosporins for each bacterial group.

Modification of the naphthalene moiety in the side chain resulted in unchanged or increased potency against Gram-positive microorganisms. The data presented in Table 3 show that the presence of an oxygen atom in the side chain, as in the case of naphthoxyacetyl cephalosporin (4A, 10A), improves activity as compared with acetyl analogues (3A, 8A). Introduction of a sulphur atom present in naphthyl thioacetyl derivatives (1B, 2B) does not significantly change the activity as compared with that of their analogues. Marked improvement in activity against Gram-positive organisms is achieved by incorporating a carbonylthiomethyl moiety into the side chain (4B). It is interesting to note that, at a concentration of $\leqslant 0.19\,\mu g/ml$, 4B shows an inhibition of 94% of *Staphylococcus* and at a concentration of $6.25\,\mu g/ml$ an inhibition of 83% of Enterococcus, while Enterococcus is generally cephalosporin resistant[10~12]. Indeed cephalexin and cephazolin, tested as reference compounds in our

Table 1.

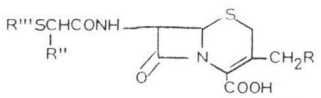


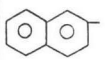
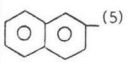
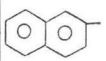
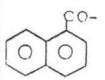
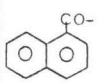
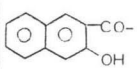
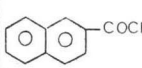
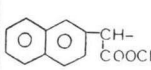
Compounds	Type Compounds	R	R'	Empirical formula	M.p.	Solvent of crystallization	NMR (δ)
1A	II[a]	H		$C_{19}H_{16}N_2O_4S$	135-137°C	$CHCl_3$ - CCl_4	9.56[b] (1H,d, -NHCO-);8.50-7.40 (7H,m,naphthyl)
2A	II[a]	H		$C_{19}H_{16}N_2O_5S$	168°C(dec.)	Et_2O - Hexane	9.53[b] (1H,d,-NHCO-);8.33-7.50(6H,m,naphthyl)
3A	II[a]	H		$C_{20}H_{18}N_2O_4S$	182-184°C	MeCOMe-Et_2O-Light petr.	8.35[b] (1H,d,-NHCO-);7.86-7.00(7H,m,naphthyl);3.71(2H,s,-CH_2CO-)
4A	II[a]	H		$C_{20}H_{18}N_2O_5S$	163-166°C	CH_2Cl_2-Et_2O-Hexane	8.15-7.13(8H,m,naphthyl and-NHCO[b]);4.76(2H,s,-OCH_2CO-);($CDCl_3$)
5A	II[a]	H		$C_{20}H_{18}N_2O_5S$	98-102°C	AcOEt - Hexane	8.50[b] (1H,d,-NHCO-);8.00-7.33(7H,m,naphthyl);5.30(1H,b,-CH-) OH
6A	II[a]	H		$C_{20}H_{17}N_5O_4S$	155°C(dec.)	AcOEt - Hexane	9.50[b] (1H,d,-NHCO-);8.20-7.40(7H,m,naphthyl);5.36(1H,s, -CH-) N_3
7A	II[a]	H		$C_{20}H_{22}N_2O_4S$	168-170°C	MeCOMe-Light petr.	8.87[b] (1H,d,-NHCO-);5.73(2H,s,-CH=CH-);5.60(1H,s,-CH=C<); 2.93(2H,s,-CH_2CO-);2.63(8H,s,-CH_2CH=)
8A	II[a]	OAc		$C_{22}H_{20}N_2O_6S$	173-175°C	MeCOMe-Light petr.	8.45[b] (1H,d,-NHCO-);7.88-7.12(7H,m,naphthyl);3.70(2H,s,-CH_2CO-)
9A	II[a]	OAc		$C_{22}H_{19}BrN_2O_6S$	125-130°C	AcOEt - Hexane	9.60[b] (1H,d,-NHCO-);8.23-7.43(7H,m,naphthyl);5.95(1H,s,-CH-) Br
10A	II[a]	OAc		$C_{22}H_{20}N_2O_7S$	131°C(dec.)	$CHCl_3$ -CCl_4	8.15-7.15(8H,m,naphthyl and-NHCO[b]);4.74(2H,s,-OCH_2CO-);($CDCl_3$)

a) These compounds were prepared by method "A" as outlined in Scheme I

b) Disappeared after D_2O exchange

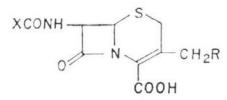
Table 2.

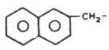
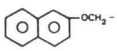
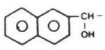
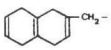
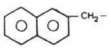
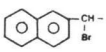
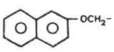
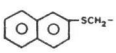
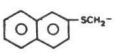
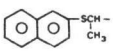
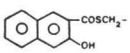
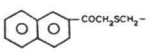
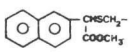


Compounds	Type Compounds	R	R''	R'''	Empirical formula	M.p.	Solvent of crystallization	NMR (δ)
1B	IV [a]	H	H		$C_{20}H_{18}N_2O_4S_2$	159-161°C	Et_2O - Hexane	9.25 [b] (1H,d,-NHCO-);7.90-7.33(7H,m,naphthyl);3.80(2H, s,-OCH_2CO-)
2B	IV [a]	OAc	H		$C_{22}H_{20}N_2O_6S_2$	145°C(dec.)	MeCN	8.40 [b] (1H,d,-NHCO-);8.00-7.33(7H,m,naphthyl);3.90(2H, s,-SCH_2CO-);(CD_3COCD_3)
3B	IV [a]	OAc	CH_3		$C_{23}H_{22}N_2O_6S_2$	105°C(dec.)	AcOEt-Hexane	9.26 [b] (1H,d,-NHCO-);8.10-7.40(7H,m,naphthyl);4.20(1H, q,-CH-);1.46(3H,d,-CH-) CH_3 CH_3
4B	IV [a]	OAc	H		$C_{23}H_{19}N_2O_7S_2^*Na$	190-192°C	MeOH - i-PrOH	9.33 [b] (1H,d,-NHCO-);8.53-7.17(7H,m,naphthyl);4.03(2H, s,-SCH_2CO-)
5B	IV [a]	OAc	CH_3		$C_{24}H_{22}N_2O_7S_2$	120-121°C	AcOEt-Et_2O-Light petr.	8.13 [b] (1H,d,-NHCO-);8.51-7.15(7H,m,naphthyl);4.83(1H, q,-CH-);1.66(3H,d,-CH-) CH_3 CH_3
6B	IV [a]	OAc	H		$C_{23}H_{20}N_2O_8S_2$	123-125°C	AcOEt-Et_2O-Light petr.	9.33 [b] (1H,d,-NHCO-);8.43-7.33(6H,m,naphthyl);4.00(2H, s,-SCH_2CO-)
7B	IV [c]	OAc	H		$C_{24}H_{22}N_2O_7S_2$	143-145°C	AcOEt-Hexane	9.16 [b] (1H,d,-NHCO-);8.80-7.53(7H,m,naphthyl);4.40(2H, s,  $COCH_2S$-);3.40(2H,s,-SCH_2CO-)
8B	IV [c]	OAc	H		$C_{25}H_{24}N_2O_8S_2$	130°C(dec.)	AcOEt - Hexane	8.13 [b] (1H,d,-NHCO-);8.10-7.30(7H,m,naphthyl);5.13(1H, s,-CHS-);3.26(2H,d,-SCH_2CO-);2.15(3H,s,-$COOCH_3$) $COOCH_3$

a) These compounds were prepared by method "B" as outlined in Scheme I
b) Disappeared after D_2O exchange
c) These compounds were prepared by method reported in experimental section
*) Isolated as sodium salt.

Table 3. Susceptibility of 89 clinical isolated to 18 new cephalosporins.



Compounds	R	X	Staphylococcus aureus (19)[a]	Enterococcus spp. (6)	Escherichia coli (22)	Salmonella spp. (10)	Klebsiella spp. (10)	Proteus mirabilis (12)	Pseudomonas aeruginosa (10)
			≤0.19[b]	6.25	50	50	50	50	100
1A	H		2		2				8
2A	H		5		2	3	1		8
3A	H		10		2				3
4A	H		14		1	2	1		5
5A	H		9			1	1		8
6A	H		13						7
7A	H		3						5
8A	OAc		10			1			6
9A	OAc		4		5		5	4	8
10A	OAc		14	2		1	1		8
1B	H		13				2	3	3
2B	OAc		9	1		1		1	4
3B	OAc		12	1					7
4B	OAc		18	5				1	9
5B	OAc		10				1	5	2
6B	OAc		11		3	7	3	5	6
7B	OAc		12	1			3	2	5
8B	OAc		5		2	2	1	1	4

a Numbers in parenthesis indicate number of isolated strains
b Concentration (μg/ml) of the tested cephalosporins

screening, exhibited MIC values of $>100\,\mu$g/ml and $100\,\mu$g/ml, respectively, in all Enterococcus tested strains.

In general, the other structural changes in the side chain do not strongly affect *in vitro* activity.

From the data listed in Table 3, it can also be seen that some of these new cephalosporins have a measurable activity even against Gram-negative bacteria. This property appears to be related to the presence of some electronegative groups.

The effect of placing a polar group, such as Br, in the α-position of the naphthylacetyl side chain has a relatively significant effect on the Gram-negative activity (9A related to 8A). The concentration of 9A required for 50% inhibition of *Klebsiella* tested strains was 50μg/ml. In particular, hydroxylation at the *ortho*-position of naphthoyl cephalosporin (2A) improves the activity against *Salmonella* and *Klebsiella* compared to that of 1A. Analogously, the 3-hydroxy-2-naphthoylthiocephalosporin (6B) inhibits a higher number of Gram-negative tested strains than does the corresponding parent compound (4B). Furthermore, of the cephalosporins discussed in this paper, 6B displays the best activity against Gram-negative microorganisms. In fact it shows an inhibition of 70% of *Salmonella* and 66% of *Proteus mirabilis* tested strains at a concentration of 50μg/ml. Moreover, a reasonable activity is maintained against Gram-positive microorganisms. Therefore, the structure of this cephalosporin appears to be compatible with broad-spectrum activity. In general, the data of the present study are in agreement with our premise that the appearance of activity against Gram-negative microorganisms is partially due to a change of the lipophilic character of the molecule.

Experimental Section

All melting points were determined in open capillary tubes, using a Buchi SMP-20 apparatus. IR spectra were obtained in KBr using a Beckman IR 20 infrared spectrophotometer; NMR spectra were obtained in DMSO-d_6 (unless otherwise indicated) on a Varian T-60 spectrophotometer. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values. Solvent evaporations were performed under reduced pressure below 40°C. Na_2SO_4 was used as the drying agent for organic extracts. The yields were between 45% and 75%.

Preparation of α-hydroxy-naphthaleneacetic acid

A solution of α-bromo-2-naphthaleneacetic acid (0.80 g, 0.003 mol) in 15% NaOH (10 ml) was heated under reflux for 5 hours. The mixture was then cooled to 0~5°C, layered with ethyl ether (50 ml) and the pH adjusted to 2~3 with conc.HCl. The organic layer was washed with water saturated NaCl, dried and evaporated *in vacuo*. The residual crude product was crystallized from benzene, m.p. 157~158°C, yield 64%. NMR: δ 8.00~7.33 (7H, m, naphthyl); 5.30 (1H, s, –CH(OH)–), Anal.: ($C_{12}H_{10}O_3$) C, H.

Preparation of compound type II: method "A"

Example: 7-[(α-Hydroxy)-2-naphthaleneacetamido] desacetoxy cephalosporanic acid (5A Table 1).

To a stirred suspension of α-hydroxy-2-naphthaleneacetic acid (0.30 g, 0.0015 mol) in dry benzene, dichloroacetyl chloride (0.5 ml, 0.005 mol) was added. The mixture was heated at 80°C for 3 hours and then thionyl chloride (1 ml, 0.013 mol) was added to the reaction solution. This solution was stirred for a further 3 hours at the same temperature. After removal of volatile material *in vacuo*, the crude O-dichloroacetyl-acid chloride was washed with dry ethyl ether (2×10 ml) and evaporated to dryness *in vacuo*. To a cooled and stirred solution of 7-ADCA (0.40 g, 0.0016 mol) and $NaHCO_3$ (0.52 g, 0.006 mol) in water (20 ml) and acetone (40 ml), O-dichloroacetyl-acid chloride dissolved in dry acetone (5 ml) was added dropwise. The reaction mixture was then stirred at room temperature overnight. The acetone was removed *in vacuo* and the pH of the aqueous solution was adjusted to 3 with conc.HCl at 0°C. The resulting precipitate was extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with water, dried and evaporated under reduced pressure to dryness. The residual crude product was crystallized from ethyl acetate - hexane to give pure compound, m.p. 98~102°C. Anal. ($C_{20}H_{18}N_2O_5S$) C, H, N, S.

Preparation of 3-hydroxy-2 thionaphthoic acid

To 3-hydroxy-2-naphthoic acid (1.90 g, 0.01 mol) was added dichloroacetyl chloride (3 ml, 0.03 mol). The mixture was stirred for 1 hour at 80°C. Subsequently, thionyl chloride (4.5 ml, 0.06 mol) was added and the resulting solution was allowed to reflux for 3 hours. The mixture was evaporated *in vacuo*. The residual crude O-dichloroacetyl-acid chloride was added drop-wise to a saturated solution of $NaHS \cdot xH_2O$ (4.5 g) in ethanol 95% (15 ml). The mixture was stirred at 15°C for 1 hour. The precipitated sodium chloride was quickly filtered off. The filtered solution was evaporated to dryness *in vacuo* yielding the crude sodium salt of the title thiolacid, which was taken up with cold water (10 ml).

The pH was adjusted to 3 with conc.HCl and the solution was extracted with ethyl ether (3 × 10 ml). The combined organic layers were washed with water, dried and evaporated *in vacuo* to give crude 3-hydroxy-2-thionaphthoic acid which was used without further purification for the next reaction.

Preparation of compounds type IV: method "B"

Example: 7-(3-Hydroxy)-2-thionaphthoylacetamido cephalosporanic acid (6B Table 2).

To a vigorously stirred solution of 7-bromoacetamido cephalosporanic acid (3.93 g, 0.01 mol) in 0.4 N $NaHCO_3$ (50 ml) and acetone (10 ml), 3-hydroxy-2-thionaphthoic acid (2.04 g, 0.01 mol) in dry acetone (15 ml) was added. After 15 hours at room temperature, the solution was concentrated *in vacuo* to eliminate acetone, then the pH was adjusted to 3 with conc.HCl at 0°C. The resulting precipitate was collected by filtration and dried. The crude product was recrystallized from ethyl acetate-light petroleum yielding pure compound, m.p. 123~125°C. Anal. ($C_{19}H_{16}N_2O_4S$) C, H, N.

Preparation of 2-naphthalene methyl acetate-α-mercaptoacetic acid

α-Bromo-2-naphthaleneacetic acid (1.30 g, 0.005 mol), dry methanol (25 ml), and conc.H_2SO_4 (1 ml) were heated under reflux for 12 hours. The volatile material was then removed *in vacuo*. The crude residue was taken up with water and extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with a concentrated solution of sodium bicarbonate and water, dried and concentrated *in vacuo*. The crude product without further purification was added to a stirred solution of mercaptoacetic acid (0.3 ml, 0.044 mol) and triethylamine (0.61 ml, 0.0044 mol). The triethylamine hydrochloride which precipitated was filtered off. The filtered solution was concentrated *in vacuo* to give a crude solid which was taken up with ethyl acetate and washed with water, dried and evaporated to dryness to yield a yellow solid, crystallized from ethyl acetate-hexane, m.p. 112~115°C, NMR: δ 8.10~7.30 (7H, m, naphthyl); 5.13 (1H, s, $-\underset{\text{COOCH}_3}{\underset{|}{\text{CH}}}\text{S}-$); 3.26 (2H, broad, $-\underset{\text{COOH}}{\underset{|}{\text{CH}_2}}\text{S}-$); 2.15 (3H, s, $-COOCH_3$). Anal ($C_{15}H_{14}O_4S$) C, H, S.

Preparation of 7-[2-naphthalene methyl acetate-α-mercaptoacetamido] desacetoxy cephalosporanic acid (8B Table 2)

To a cooled (0~5°C) solution of 2-naphthalene-methylacetate-α-mercaptoacetic acid (0.60 g, 0.002 mol) in dry ethyl ether (10 ml), PCl_5 (0.40 g, 0.002 mol) was added, in one portion, and the temperature was allowed to reach 15~20°C.

After 4 hours, the volatile material was evaporated *in vacuo*. The residual crude acid chloride was taken up with dry acetone (5 ml) and added dropwise to a cold, stirred solution of 7-ADCA (0.50 g, 0.002 mol) in 0.1 N $NaHCO_3$ (30 ml) and acetone (70 ml). The mixture was then stirred at room temperature overnight. The acetone was removed *in vacuo* and the pH was adjusted to 3 with conc.HCl at 0°C. The resulting precipitate was extracted with ethyl acetate (3 × 30 ml). The combined organic layers were washed with a concentrated NaCl solution, dried, filtered and evaporated to dryness under reduced pressure. The residual crude product was crystallized from ethyl acetate-hexane to give pure compound, m.p. 130°C (dec.) Anal. ($C_{23}H_{24}N_2O_8S_2$) C, H, N, S.

Preparation of α-(2-acetonaphthone)-mercaptoacetic acid

To a solution of α-bromo-2-acetonaphthone (1.3 g, 0.005 mol) and $NaHCO_3$ (0.84 g, 0.01 mol) in water (50 ml) and acetone (50 ml), mercaptoacetic acid (0.35 ml, 0.005 mol) was added. The mixture was allowed to react at room temperature for 2 days. After evaporation of the acetone, the alkaline aqueous solution was washed with ethyl ether (3 × 30 ml, which was discarded) and then the pH

adjusted to 2~3 with 2 N HCl. This aqueous solution was extracted with ethyl acetate (3 × 50 ml). The combined extracts were washed with water, dried and evaporated *in vacuo*. The residual crude product was crystallized from carbon tetrachloride, m.p. 80~81°C, yield 55%. NMR: δ 8.80~7.50 (7H, m, naphthyl); 4.33 (2H, s, $-COCH_2S-$); 3.40 (2H, s, $-SCH_2CO-$). Anal. ($C_{14}H_{12}O_3S$) C, H, S.

Preparation of 7-[α-(2-acetonaphthone) mercaptoacetamido] cephalosporanic acid (7B Table 2)

The product was obtained in a manner similar to that described in the previous section.

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