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Microbial reduction of ω-bromoacetophenones in the presence of surfactants

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Abstract

Several ω-bromoacetophenone derivatives **6a–f** were reduced to (*R*)-(−)-2-bromo-1-(phenyl/substituted phenyl) ethanol derivatives **7a–f** with whole cell biocatalysts in good yields. The enantiomeric excesses were increased to 95% using an anionic surfactant under an inert atmosphere in an aqueous medium.

1. Introduction

Many 2-substituted amino-1-arylethanols **1** are intermediates for important adrenergic drugs and drug candidates.[1] The biological activity of **1** resides mostly in their (*R*)-enantiomers while the (*S*)-enantiomer is generally less active and sometimes exhibits side effects.[2] Because of stringent guidelines set by the US Food and Drug Administration[3] and the potential industrial applications, the preparation of enantiomerically pure chiral drugs and drug intermediates is currently gaining momentum. The general strategy for the preparation of enantiomerically enriched 2-amino-1-arylethanols **1** is to hook up a suitable amine to an enantiomerically enriched aryl oxirane **2** or to reduce an enantiomerically enriched nitrile **3** prepared through a chemical or biocatalytic pathway. Most of the chiral arylethanols **7a–f**, the syntheses of which are discussed in this paper, are important intermediates in the preparation of important pharmaceuticals,[4] pesticides,[5] artificial sweeteners[6] and other industrially important products.[7]

The non-racemic aryl oxirane **2** can be prepared from chiral 2-bromo-1-arylethanol **5** through asymmetric reduction of ω-bromoketone **4** with chiral homogeneous catalysts and hydrogen.[8] However, the high cost of such homogeneous catalysts and their poor recovery make the process expensive. In another strategy the carbonyl group of a ω-bromoacetophenone **4** is reduced with borohydride and then the racemic ethanol is resolved by lipase-mediated transesterification.[1]

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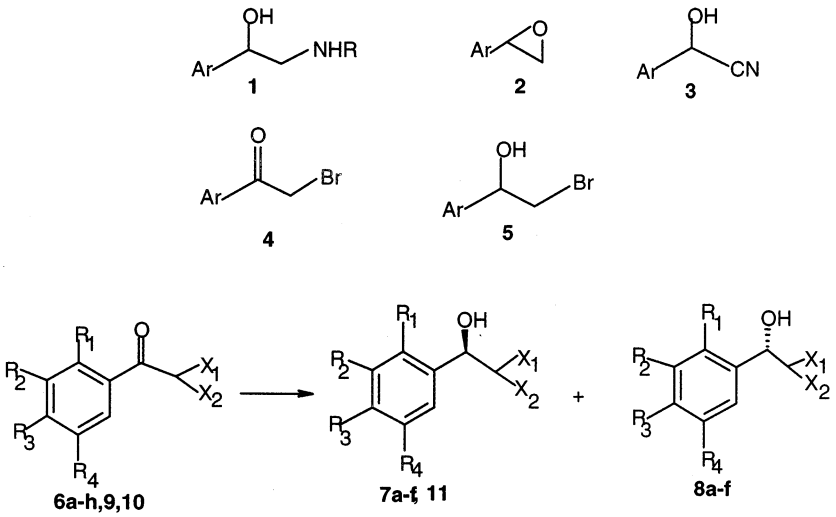
The use of biotransformation methods by enzymes or whole-cell microbial systems results in high enantioselectivity under mild and environmentally-friendly conditions.[9] Enzymatic biotransformations give both higher yields and enantioselectivities than whole-cell microbial systems. However, the isolated enzymes require recycling of costly cofactors. On the other hand, the whole microbial cells contain several dehydrogenases which are able to accept non-natural substrates and contain all the necessary cofactors and metabolic pathways for their regeneration.[10] Keeping this in mind, we investigated the preparation of (*R*)-(−)-2-bromo-1-(phenyl/substituted phenyl) ethanol **7a–f** from ω-bromoacetophenones **6a–f** (Scheme 1) by reduction with whole microbial cells of three microorganisms, namely *Rhodotorula rubra* (RB-2), *Candida tropicalies* (RB-3) and *Saccharomyces cerevisiae* (RB-4), isolated from local brewery waste, municipal dumping grounds and compost heaps. The organisms were identified in the laboratory on the basis of physiological, biological and morphological tests. We selected phenacyl bromide **6a** as the model compound to establish the optimum conditions to achieve maximum yield and enantioselectivity of arylethanols **7a–f** from **6a–f**. For that purpose we manipulated the reaction conditions to achieve our goal and now report an efficient method for reducing **6a** to **7a** in particular and **6b–f** to **7b–f** in general by the microbe *R. rubra* in an environmentally-friendly way.[11–13]



a, $X_1=R_1=R_2=R_3=R_4=H$, $X_2=Br$

b, $X_1=R_1=R_2=R_3=H, R_4=Cl, X_2=Br$

c, $X_1=R_1=R_2=R_4=H$, $R_3=PhCH_2O$, $X_2=Br$

d, $X_1=R_1=R_2=H, R_3=PhCH_2O, R_4=CH_2OH, X_2=Br$

e, $X_1=X_2=Br, R_1=R_2=H, R_3=PhCH_2O, R_4=CH_2OH$

f, $X_1=R_1=R_2=H, R_3=R_4=$-O-CH_2-O-CH_2-, $X_2=Br$

g, $X_1=X_2=R_3=H, R_1=OH, R_2=Br$, $R_4=CH_3$

h, $X_1=R_2=R_3=H, R_4=CH_3, R_1=OH, X_2=Br$

9, $X_1=R_1=R_2=R_3=R_4=H, X_2=OH$

10 & 11, $X_1=X_2=R_1=R_2=R_3=R_4=H$

Scheme 1.

2. Results and discussion

Phenacyl bromide **6a** was reduced to (*R*)-(−)-2-bromo-1-phenyl ethanol **7a** by microbial reduction with *R. rubra* in water in moderate yield (70%) and ee (61%). *C. tropicalies* and *S. cerevisiae* also produced **7a** but in low yield (<40%) and ee (24–31%) (Table 1). The use of hydrophobic organic solvents has been reported to be useful in reversing the enantioselectivity in microbial reactions.[14] Along this line we tried the experiments in several hydrophobic solvents so as to reverse the enantioselectivity to the (*R*)-form in *C. tropicalies* and *S. cerevisiae*. Neither microbe, however, reacted at all in hydrophobic organic solvents (Table 1). None of the three microbes converted **6a** to **7a** in hydrophobic organic solvents (Table 1) as has been reported in the case of some other microorganisms.

The preliminary screening of the three microorganisms prompted us to select *R. rubra* as the microorganism of choice for our purpose. To improve the reaction several manipulations, e.g. effect of light, gas, immobilisation and surfactant were carried out.

The exposure of the reaction media to a 150 W glowing bulb produced several unidentified minor products. Adsorption of whole cells of a microorganism on a solid surface is a technique for immobilisation. In our attempt to study the effect of immobilisation of *R. rubra* the whole cell body of the microorganism was entrapped on calcium alginate and used in the biotransformation of **6a** to **7a**. We found that the yield (40%) and ee (33%) were worse than under the normal conditions. This behaviour has also been observed before.[15a]

The use of surfactants has found use in enzymatic biotransformation reactions. However, to the best of our knowledge, no such studies have been reported thus far in the case of whole cell microbial reactions. We studied the effect of both anionic (sodium lauryl sulphate, SLS) and cationic (cetyl trimethyl ammonium bromide, CTAB) surfactants. For this purpose the substrate **6a** was first adsorbed on the surfactant at a substrate:adsorbant ratio of 1:3 and then allowed to undergo microbial reduction by *R. rubra*. CTAB produced ω-hydroxyacetophenone **9** only. A control experiment in absence of *R. rubra* was carried out which also produced only **9** confirming the role of CTAB in the hydrolysis of **6a** to **9**. The reason why **7a** was not formed at all is not clear. The role of a micelle is to bring reactants together

Table 1
Microbial reduction in different solvents

Microorganism	Solvent	Time (h)	Yield (%)	*R*/*S*	ee (%)
RB-2	Water	30	70	*R*	61
	Benzene	120	nil		
	Dichloromethane	120	nil		
	Petroleum ether	120	nil		
RB-3	Water	48	20	*R*	24
	Benzene	120	nil		
	Dichloromethane	120	nil		
	Petroleum ether	120	nil		
RB-4	Water	48	40	*R*	31
	Benzene	120	nil		
	Dichloromethane	120	nil		
	Petroleum ether	120	nil		

and speed up the reaction or to keep them apart and inhibit it.[15b] Probably CTAB did not entrap the reactants in such a way to make the enzymatic reaction possible.[15c] Although ionic micelles generally inhibit hydrolysis reactions, cationic micelles are reported to catalyse hydrolysis of certain compounds.[15c] In our case probably CTAB did not bring the substrate and the whole-cell microbe together for reduction, but facilitated the hydrolysis of **6a**. However, SLS which probably entrapped the substrate and the whole-cell microbe together for the reaction made a major improvement in both the yield (90%) and ee (95%) of (*R*)-(−)-**7a**. The microbial reduction also caused considerable improvements in yield and ee in the case of **7b–f** (Table 2). The reaction did not proceed in the case of **6g** and **6h** where both the substrates have free phenolic groups.

Table 2
Microbial reduction in presence of anionic surfactant

Substrate[a]	Surfactant	Product	Time (h)	Yield (%)	Configuration	ee (%)[d]
6a	CTAB[b]	**9**	30	87	–	–
6a	SLS[c]	**7a**	30	90	*R*	95
6b	SLS	**7b**	48	77	*R*	95
6c	SLS	**7c**	48	81	*R*	94
6d	SLS	**7d**	48	79	*R*	95
6e	SLS	**7e**	40	82	*R*	92
6f	SLS	**7f**	72	69	*R*	89
6g	SLS	–	140	–	–	–
6h	SLS	–	140	–	–	–

[a] The reaction was carried out in an argon atmosphere.
[b] CTAB, cetyl trimethyl ammonium bromide.
[c] SLS, sodium lauryl sulphate.
[d] Absolute configuration and ee were determined by HPLC analysis of the Mosher's ester[17] in a Chiralcel OD column of 250 × 46 mm i.d., particle size 10 μm using 15% 2-propanol in hexane as the mobile phase; flow rate: 1 ml/min; retention times: 9 min for (*S*)-**8a**, 9.6 min for (*R*)-**7a**, 21.5 min for (*S*)-**8b**, 23.3 min for (*R*)-**7b**, 18 min for (*R*)-**7c**, 20 min for (*S*)-**8c**, 11.35 min for (*R*)-**7d**, 12.6 min for (*S*)-**8d**, 8.94 min for (*R*)-**7e**, 11.04 min for (*S*)-**8e**, 9.99 min for (*S*)-**8f** and 10.44 min for (*R*)-**7f**.

The effect of several gases on the microbial reaction of *R. rubra* on **6a** in the presence of SLS was studied.[16] It was found that the reaction was best in yield (90%) and ee (95%) in an atmosphere of argon (Table 2), while in aerobic conditions it was moderate (Table 1).

3. Conclusion

In summary, a simple and general microbial and environmentally-friendly method has been developed that allows the preparation of (*R*)-(−)-2-bromo-1-arylethanols **7a–f** in high yields (69–90%) and ees (89–95%) under mild conditions by whole cells of *R. rubra* in the presence of SLS and argon in aqueous media under neutral conditions (pH 7).

4. Experimental

4.1. Materials and methods

Organic chemicals were purchased from Aldrich unless otherwise indicated. ^{1}H NMR spectra (in $CDCl_3$) were recorded on Varian T-60 and Avance DPX 300 MHz Bruker spectrometers. Chemical shifts are given in parts per million (ppm) with TMS as the internal standard. Enantiomeric excesses were determined by HPLC analysis of the Mosher's esters[17] on a Waters Modular HPLC instrument using a Chiralcel OD column (4.6×250 mm i.d.) from Daicel Chemical Company, optical rotation data were recorded on a Perkin–Elmer model 343 digital polarimeter, IR spectra on a Perkin–Elmer model 237B spectrometer, mass spectra on an AEI Finnigan Mat spectrometer and C,H analysis on a Perkin–Elmer 2400 instrument. The anaerobic incubations with specific gases in the microbial reactions were carried out in a two-necked flat-bottomed glass vessel having gas inlet and outlet provisions. The gas inlet had its stem elongated with the end dipped in the reaction medium. Both the inlet and outlet tubes were fitted with stop cocks to regulate the flow of gas.

The microorganisms RB-2, RB-3 and RB-4 belong to the Biochemistry Division collection of this laboratory.

4.2. Preparation of substrate ***6a–h***

The brominated derivatives **6a–h** were obtained as reported in the literature[18] from the corresponding acetophenone derivatives. 4-Hydroxy-3-hydroxymethyl acetophenone and 6-acetyl-1,3-benzodioxan and their corresponding benzyloxy derivatives were prepared according to the literature.[19]

4.3. Microorganisms, media and culture conditions

4.3.1. Culture media

Two culture media of different compositions were employed. Medium A consisted of (g/l): malt extract 3; yeast extract 3; peptone 5; and glucose 10. The final pH of the medium was adjusted to 7.0. Medium B consisted of (g/l): K_2HPO_4 0.5; $(NH_4)SO_4$ 1.2; yeast extract 5 and glucose 10. The pH of the medium was adjusted to 5.0 before autoclaving.

4.3.2. Culture conditions

All three cultures were grown in 250 ml Erlenmeyer flasks containing 40 ml of media on a rotary shaker. Culture medium A was used for *C. tropicalies* and *R. rubra* whereas medium B was used for *S. cerevisiae*. The shaker was set with an agitation of 200 rpm and a constant temperature of 30°C. A preinoculate was grown with a loopfull of respective strain in the culture media from the agar slant. After 20 h of growth 1 ml of the cell suspension in the cell culture media was transferred aseptically to each flask. Fresh cells from the submerged cultures were centrifuged and washed with 0.1 M phosphate buffer (pH 7). Washed cells were used directly for biotransformations.

4.4. General procedure for whole cell microbial reduction of ω-bromoacetophenones under an aerobic atmosphere

4.4.1. Preparation of (R)-(−)-2-bromo-1-phenyl ethanol **7a**

Phenacyl bromide **6a** (0.2 g, 1 mmol) was added to a suspension of freshly prepared wet whole cells of *R. rubra* (10 g) in water (200 ml) maintaining the pH of the reaction mixture at 7.0 and shaken (200 rpm) for 30 h at 30°C. The reaction mixture was extracted in ethyl acetate (3×50 ml) and then dried over anhydrous sodium sulphate. The solvent was then removed under reduced pressure and the product was purified by passing it through a small silica gel column using 3:1 petroleum ether/dichloromethane as the eluent. Yield: 0.14 g (70%) of (*R*)-(−)-2-bromo-1-phenyl ethanol **7a**.[20] ^{1}H NMR δ: 2.2 (1H, O*H*, bs), 3.19 (2H, CH_2Br, m), 4.4 (1H, C*H*OH, dd, $J=8$ and 4 Hz) and 6.9 (5H, aromat. *H*, s); IR (KBr, cm^{-1}): 3300, 2930, 1540, 1200; EIMS m/z: 200 (M$^+$), 202; $[\alpha]^{25}$ −24 (*c* 4, CH_2Cl_2) (lit.[20] −39).

The same procedure was repeated for the microbial reduction with *C. tropicalies* (RB-3) and *S. cerevisiae* (RB-4). Yield of **7a**: 20% with RB-3 and 40% with RB-4.

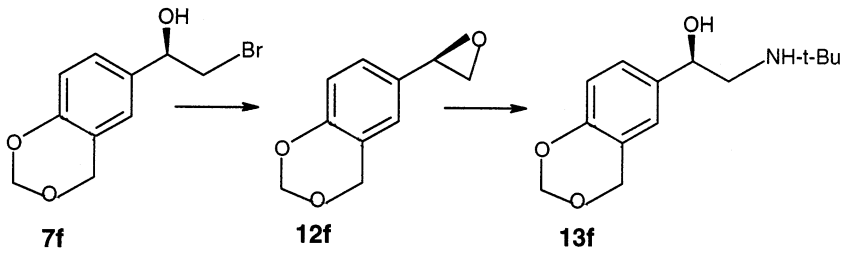
4.4.2. Whole cell microbial reduction of ω-bromoacetophenones adsorbed on surfactants: preparation of (R)-(−)-2-bromo-1-phenyl ethanol **7a** under an argon atmosphere

Phenacyl bromide **6a** (0.2 g, 1 mmol) was first dissolved in acetone and then added to 0.6 g of SLS in a 1:3 ratio and stirred for 10 min. The solvent was removed under reduced pressure and the solid obtained was added to 10 g of the wet microbial cell of *R. rubra* in 200 ml water while maintaining the solution at pH 7. A total of four reaction flasks were collected. Air was driven out of the flasks and argon was added. The flasks were then placed in a shaker (200 rpm) for 30 h at 30°C. The reaction mixtures were extracted in ethyl acetate several times (4×50 ml) and the solvent was dried over anhydrous sodium sulphate. The solvent was then removed under reduced pressure. The crude product obtained was then purified by chromatography using 50% petroleum ether–dichloromethane as eluent. Yield: 0.181 g (90%) of (*R*)-(−)-2-bromo-1-phenyl ethanol **7a**. $[\alpha]^{25}$ −36 (*c* 4, CH_2Cl_2) (lit.[20] −39). The above reaction when carried out in presence of cationic surfactant CTAB under exactly the same conditions yielded ω-hydroxyacetophenone **9**; mp 88°C (lit.[22] 89°C), yield 0.19 g (87%). All the spectral data were identical with those reported in the literature.[22]

4.4.3. Under a hydrogen atmosphere

The above reaction was carried out for 30 h under a hydrogen atmosphere keeping the other conditions intact. The products **7a**, **10** and **11** were purified by column chromatography using 30% dichloromethane in petroleum ether and were characterised using IR, NMR and mass spectroscopic data and were found to be (*R*)-(−)-2-bromo-1-phenyl ethanol, acetophenone and (S)-1-phenyl ethanol.[21] The isolated yields of **7a**, **10** and **11** were 10, 17 and 45%, respectively. $[\alpha]_D^{25}$ of **11**: −50 (*c* 4, CH_2Cl_2) (lit.[21] −49.3).

*4.4.3.1. Preparation of (R)-(−)-2-Bromo-1-(3′-chlorophenyl) ethanol **7b**.* Isolated yield: 77%; oil; $[\alpha]_D^{25}$ −9.1 (*c* 4, CH_2Cl_2); ^{1}H NMR δ: 1.9 (1H, OH, bs), 3.35 (2H, CH_2Br, m), 4.5 (1H, C*H*OH, dd, $J=8$ and 3 Hz), 6.6–7.3 (4H, aromat. *H*, m); IR (KBr, cm^{-1}): 3330, 2925, 1475, 1050; EIMS m/z: 234 (M$^+$), 236, 238. Anal. calcd for C_8H_8BrClO: C, 41.02; H, 3.41; found: C, 41; H, 3.33%.



Scheme 2.

4.4.3.2. Preparation of (R)*-(+)-2-Bromo-1-(4′-benzyloxyphenyl) ethanol* ***7c***. Isolated yield: 81%; mp 70–73°C; $[\alpha]_D^{25}$ +8.5 (*c* 4, $CHCl_3$); ^1H NMR δ: 1.1 (1H, O*H*, bs), 2.1 (2H, CH_2Br, m), 4.4 (1H, C*H*OH, d, $J=8$ and 3 Hz), 5 (2H, OCH_2Ph, s), 6.7 (2H, aromat. 2-*H* and 6-*H*, dd, $J=8$ and 2 Hz), 7.7 (2H, aromat. 3-*H* and 5-*H*, dd, 8 and 2 Hz); IR (KBr, cm^{-1}): 3330, 2930, 1550, 1250; EIMS *m*/*z*: 306 (M^+), 308. Anal. calcd for $C_{15}H_{15}BrO_2$: C, 58.8; H, 4.9; found: C, 58.65; H, 4.8%.

4.4.3.3. (R)*-(+)-2-Bromo-1-(3′-hydroxymethyl-4′-benzyloxyphenyl) ethanol* ***7d***. Isolated yield: 79%; mp 118°C; $[\alpha]_D^{25}$ +25 (*c* 4, CH_2Cl_2); ^1H NMR δ: 2.7 (1H, OH of CH_2OH, bs), 3.5 (1H, OH of CHO*H*, bs), 3.63 (2H, CH_2Br, m), 4.7 (2H, CH_2OH, s), 4.87 (1H, C*H*OH, dd, $J=8$ and 4 Hz), 5.1 (2H, OCH_2Ph, s), 6.9–7.4 (8H, aromat. *H*, m); IR (KBr, cm^{-1}): 3300, 2900, 1500, 1175; EIMS *m*/*z*: 336 (M^+), 338. Anal. calcd for $C_{16}H_{17}BrO_3$: C, 57.14; H, 5.06; found: C, 56.99; H, 4.87%.

4.4.3.4. (R)*-(−)-2,2-Dibromo-1-(4′-benzyloxy-3′-hydroxymethylphenyl) ethanol* ***7e***. Isolated yield: 82%; mp 97°C; $[\alpha]_D^{25}$ −31.5 (*c* 1, CH_2Cl_2); ^1H NMR δ: 2.2 (1H, O*H* of CH_2OH, bs), 3 (1H, O*H* of CHO*H* bs), 4.55 (2H, CH_2OH, s), 4.8 (1H, C*H*Br$_2$, d, $J=8$ Hz), 4.9 (2H, OCH_2Ph, s), 5.5 (1H, C*H*OH, d, $J=8$ Hz), 6.8–7.26 (8H, aromat. *H*, m); IR (KBr, cm^{-1}): 3340, 2950, 1500, 1200; EIMS *m*/*z*: 414 (M^+), 416. Anal. cacld for $C_{16}H_{16}Br_2O_3$: C, 46.3; H, 3.86; found: C, 46.22; H, 3.56%.

4.4.3.5. (R)*-(−)-2-Bromo-1-(1,3-benzodioxan-6-yl) ethanol* ***7f***. Isolated yield: 69%; mp 67°C; ^1H NMR δ: 1.66 (1H, O*H*, bs), 2.1 (2H, CH_2Br, m), 4 (1H, C*H*OH, dd, $J=9$ and 3 Hz), 4.75 (2H, C–CH_2–O, s), 5.1 (2H, O–CH_2–O, s), 6.7 (1H, aromat. 8-*H*, d, $J=8$ Hz), 7.4 (1H, aromat. 5-*H*, d, $J=4$ Hz), 7.5 (1H, aromat. 7-*H*, dd, $J=8$ and 2 Hz); IR (KBr, cm^{-1}): 3330, 2925, 1530, 1135; EIMS *m*/*z*: 258 (M^+), 260. Anal calcd for $C_{10}H_{11}BrO_2$: C, 46.51; H, 4.26; found: C, 46.44; H, 4.26%.

4.4.4. Determination of the absolute configuration of ***7f***

(*R*)-(−)-1-(1,3-benzodioxan-6-yl)-2-(*tert*-butyl amino) ethanol **13f** was obtained from **7f** (Scheme 2). Compound **7f** (0.5 g, 1.9 mmol) and 0.21 g (3.8 mmol) of KOH were dissolved in 30 ml of diethyl ether and refluxed for 1 h. The reaction mixture was cooled and washed with water (3×25 ml) and then dried over anhydrous sodium sulphate. The solvent was removed

under reduced pressure to obtain 0.25 g of epoxide **12f**. This was then transferred into a closed glass tube with 3 ml of *t*-butyl amine and heated for 4 h at 100°C. After cooling, the excess reagent was evaporated under reduced pressure and the residue obtained was purified by a silica gel chromatography (eluent: 4:1 petroleum ether/ethyl acetate). Yield: 0.19 g of **13f** (76%); mp 129°C; $[\alpha]_D^{25}$ −23 (*c* 1, CH_2Cl_2) (lit.[4a] −24); ^{1}H NMR δ: 1.2 (9H, $3CH_3$, s), 2.48 (2H, CH_2NBu^t), 4.67 (1H, CHOH, dd, $J=9$ and 3.6 Hz), 4.77 (2H, C–CH_2–O, s), 5.23 (2H, O–CH_2–O, s), 6.80 (1H, aromat. 7-*H*, d, $J=8.4$ Hz), 7.00 (1H, aromat. 5-*H*, d, $J=1.2$ Hz), 7.2 (1H, aromat. 8-*H*, dd, $J=8.4$ and 1.2 Hz). Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57; found: C, 66.85; H, 8.37; N, 5.50%.

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