International Journal of Chemical, Materials and Biomolecular Sciences
ISSN: 2415-6620
Vol:9, No:4, 2015

Improvement of Reaction Technology of Decalin Halogenation

Dmitriy Yu. Korulkin, Ravshan M. Nuraliev, Raissa A. Muzychkina

***Abstract*—**In this research paper were investigated the main regularities of a radical bromination reaction of decalin. There had been studied the temperature effect, durations of reaction, frequency rate of process, a ratio of initial components, type and number of the initiator on decalin bromination degree.

There were specified optimum conditions of synthesis of a perbromodecalin by the method of a decalin bromination. There are developed the technological flowchart of receiving a perbromodecalin and the mass balance of process on the first and the subsequent loadings of components.

The results of research of antibacterial and antifungal activity of synthesized bromoderivatives have been represented.

***Keywords*—**Decalin, optimum technology, perbromodecalin, radical bromination.

I. Introduction

PERFTORANUM, being a blood substitute with function of oxygen transport, is widely applied at a sharp and chronic hypovolemia, microcirculation violation, for correction of tissue gas exchange and a metabolism at blood loss, shock of various etiology, intoxications, violations of coronary and brain blood circulation, a cardioplegia, partial perfusion.

Perftoranum is a solution used as an intravascular oxygen carrier to temporarily augment oxygen delivery to tissues. Right now, the goal of the development of perftoranum is simply to reduce the need for donor blood during surgery, but this product clearly has the potential for additional future uses. Perfluorocarbons surrounded by a surfactant and suspended in a water-based solution give perftoranum its oxygen carrying capacity. The perftoranum particles are removed from the bloodstream within 48 hours by the body's normal clearance procedure for particles in the blood. The fact that this blood substitute is synthetic gives it certain distinct advantages over blood substitutes that rely on modified hemoglobin, such as unlimited manufacturing capabilities, ability to be heat-sterilized, and the perfluoroderivatives' efficient oxygen delivery [1]-[3].

The most industrially significant semi-product in synthesis of perftoranum is the perbromodecalin [4]. Therefore, it is very important to investigate optimum conditions of decalin bromination.

Dmitry Yu. Korulkin is with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050038 Kazakhstan (corresponding author to provide phone: 727-387-1751; fax: 727-292-3731; e-mail: Dmitriy.Korulkin@kaznu.kz).

Ravshan M. Nuraliev and Raissa A. Muzychkina are with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050038 Kazakhstan (e-mail: ravsh_team@mail.ru, rmuz@mail.ru).

II. Results and Discussion

Perfluorodecalin has been received by naphthalene fluorination that is very economically unprofitable, unhandy and ecologically dangerous method.

Practical interest represents receiving a perfluorodecalin in more sparing conditions. Those are receiving it from a perbromodecalin, with the subsequent replacement of fluorine by bromine in the methods described in literature, which do not present a great difficulty. Improvement of technological parameters of a radical bromination of decalin included definition:

- composition of resultants of reaction in a stoichiometric relationship and UV-initiation;
- influences of frequency rate of reaction in a stoichiometric relationship (t=80 and 120^0C, UV-initiation) on composition of reaction resultants;
- time effects of reaction in a stoichiometric relationship to the structure of reaction products; influences of bromine excess on composition of reaction resultants;
- influences of type and concentration of the initiator on composition of reaction resultants of a reaction of decalin radical bromination;
- influences of the stabilizer on composition of reaction resultants of a decalin radical bromination; development of the technological flowchart with the indication of monitoring points.

During research, there were received 13 intermediate products of the decalin bromination and perbromoderivatives (substances I-XIV) in an individual type [5]-[8]:

2,6-dibromodecalin (I): MS m/z (70 eV): 296 $[M]^+$, 295 $[M-H]^+$, 215 $[M-H-Br]^+$, 203, 189, 188, 174, 160, 123, 120, 119, 105, 92, 90, 67, 53, 40. ^{13}C-NMR (100 MHz, $CDCl_3$): 44.1 (C-1,5); 52.8 (C-2,6); 40.5 (C-3,7); 26.3 (C-4,8); 35.1 (C-9,10).

1,5-dibromodecalin (II): MS m/z (70 eV): 296 $[M]^+$, 295 $[M-H]^+$, 215 $[M-H-Br]^+$, 203, 191, 177, 163, 149, 123, 111, 98, 97, 82, 84, 70, 56, 42. ^{13}C-NMR (100 MHz, $CDCl_3$): 54.7 (C-1,5); 40.4 (C-2,6); 21.8 (C-3,7); 16.9 (C-4,8); 39.7 (C-9,10).

1,3,5,7-tetrabromodecalin (III): MS m/z (70 eV): 454 $[M]^+$, 453 $[M-H]^+$, 373 $[M-H-Br]^+$, 361, 347, 267, 266, 254, 240, 160, 147, 134, 133, 121, 120, 106, 92, 80, 53, 41. ^{13}C-NMR (100 MHz, $CDCl_3$): 40.3 (C-1,5); 48.4 (C-2,6); 42.2 (C-3,7); 49.9 (C-4,8); 34.0 (C-9,10).

1,4,5,8-tetrabromodecalin (IV): MS m/z (70 eV): 454 $[M]^+$, 453 $[M-H]^+$, 373 $[M-H-Br]^+$, 361, 348, 347, 333, 320, 268, 255, 253, 241, 240, 227, 147, 134, 133, 121, 120, 106, 92, 80, 53, 41. ^{13}C-NMR (100 MHz, $CDCl_3$): 48.9 (C-1,4,5,8); 35.1 (C-2,3,6,7); 42.2 (C-9,10).

1,2,4,5,6,8-hexabromodecalin (V): MS m/z (70 eV): 612 $[M]^+$, 611 $[M-H]^+$, 531 $[M-H-Br]^+$, 519, 518, 427, 413, 412, 320, 307, 306, 214, 213, 121, 120, 107, 106, 92, 80, 40. ^{13}C-NMR (100 MHz, $CDCl_3$): 49.9 (C-1,5); 48.7 (C-2,6); 38.6 (C-3,7); 45.6 (C-4,8); 36.2 (C-9,10).

1,2,3,5,6,7-hexabromodecalin (VI): MS m/z (70 eV): 612 $[M]^+$, 611 $[M-H]^+$, 531 $[M-H-Br]^+$, 519, 518, 426, 425, 333, 319, 318, 226, 225, 133, 132, 92, 80, 40.^{13}C-NMR (100 MHz, $CDCl_3$): 34.8 (C-1,5); 49.2 (C-2,6); 48.3 (C-3,7); 48.8 (C-4,8); 29.8 (C-9,10).

1,2,3,4,5,6,7,8-octabromodecalin (VII): MS m/z (70 eV): 770 $[M]^+$, 769 $[M-H]^+$, 689 $[M-H-Br]^+$, 677, 584, 583, 491, 490, 398, 397, 305, 292, 291, 199, 198, 106, 105, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 45.6 (C-1,4,5,8); 44.1 (C-2,3,6,7); 31.6 (C-9,10).

1,2,2,3,4,5,6,6,7,8-decabromodecalin (VIII): MS m/z (70 eV): 928 $[M]^+$, 848 $[M-Br]^+$, 756 $[M-CBr]^+$, 755, 663, 662, 570, 569, 477, 397, 305, 304, 276, 263, 262, 170, 169, 156, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 44.9 (C-1,5); 67.1 (C-2,6); 55.6 (C-3,7); 40.1 (C-4,8); 26.8 (C-9,10).

1,2,2,3,4,4,5,6,6,7,8,8-dodecabromodecalin (IX): MS m/z (70 eV): 1086 $[M]^+$, 1006 $[M-Br]^+$, 914 $[M-CBr]^+$, 913, 821, 741, 649, 648, 556, 476, 384, 371, 370, 278, 198, 106, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 39.4 (C-1,5); 62.2 (C-2,6); 64.9 (C-3,7); 54.0 (C-4,8); 33.1 (C-9,10).

1,1,2,3,4,4,5,5,6,7,8,8-dodecabromodecalin (X): MS m/z (70 eV): 1086 $[M]^+$, 1006 $[M-Br]^+$, 914 $[M-CBr]^+$, 913, 901, 821, 741, 649, 648, 556, 476, 384, 371, 370, 358, 278, 198, 106, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 53.9 (C-1,4,5,8); 50.8 (C-2,3,6,7); 42.4 (C-9,10).

1,1,2,2,3,4,4,5,5,6,6,7,8,8,-tetradecabromodecalin (XI): MS m/z (70 eV): 1244 $[M]^+$, 1164 $[M-Br]^+$, 1072 $[M-CBr]^+$, 992, 900, 820, 728, 727, 635, 555, 463, 450, 370, 278, 198, 106, 105, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 62.8 (C-1,5); 71.9 (C-2,6); 60.5 (C-3,7); 49.6 (C-4,8); 38.4 (C-9,10).

1,1,2,2,3,3,4,5,5,6,6,7,7,8-tetradecabromodecalin (XII): MS m/z (70 eV): 1244 $[M]^+$, 1164 $[M-Br]^+$, 1072 $[M-CBr]^+$, 992, 900, 899, 820, 807, 728, 727, 635, 555, 463, 450, 370, 278, 265, 198, 185, 106, 105, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 62.6 (C-1,5); 86.1 (C-2,6); 72.9 (C-3,7); 37.2 (C-4,8); 28.2 (C-9,10).

1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-hexadecabromodecalin (XIII): MS m/z (70 eV): 1402 $[M]^+$, 1322 $[M-Br]^+$, 1230 $[M-CBr]^+$, 1150, 1058, 978, 886, 806, 714, 634, 542, 529, 449, 357, 277, 185, 105, 92, 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 58.1 (C-1,4,5,8); 82.3 (C-2,3,6,7); 33.2 (C-9,10).

Perbromodecalin (XIV): MS m/z (70 eV): 1560 $[M]^+$, 1480 $[M-Br]^+$, 1388 $[M-CBr]^+$, 1308, 1228, 1148, 1136, 976, 964, 804, 792, 780, 608, 596, 516, 436, 424, 412, 332, 240, 184, 182, 92, 80 80. ^{13}C-NMR (100 MHz, $CDCl_3$): 62.8 (C-1,4,5,8); 77.6 (C-2,3,6,7); 53.5 (C-9,10).

The GC-MS analysis was carried out on a gas chromatograph Agilent 6890 N with the mass and selection detector Agilent 5973 N and a flame ionization detector; ^{13}C NMR spectrum of synthesized substances were recorded on Bruker AMH-400 nuclear magnetic resonance spectrometer.

UV-initiation in a stoichiometric relationship of reaction reagents of a bromination leads to maximum replacement of four hydrogen atoms, regardless of process temperature [9].

However, rough evaporation of bromine at temperatures over 80^0C, makes reaction weak controllable in the technological mode, and temperature increasing over 140^0C causes a baking of reactionary mass. Thereof, as the optimum temperature of a bromination it is necessary to consider 80^0C [10]-[12].

To increase conversion level of bromine and technological controllability of process, influence of frequency rate of bromine addition during all process was studied. Frequency rate of bromine addition was changed in the range from one to five with a step 1, adding bromine in the equal portions, according to the chosen frequency rate.

To study the influence of a bromination on conversion level of decalin, synthesis was carried out in the above-described conditions from 2 to 30 hours [13].

In case of increase of reaction duration, starting from 10-hour heating the sum of hexabromdecalin begins to accumulate. Reaction reaches optimum efficiency at the 24th hour heating above which, increase of an exit the bromderivatives becomes much less essential.

Therefore, 24 hours should be considered as an optimum duration of bromination process. To study ratio components influence in reactions to conversion level of decalin, we carried out reaction in excess of bromine from 2 to 15% of the stoichiometric.

Increase of bromine content from the stoichiometric leads to increase of conversion level of decalin (from 2 to 15%), and also simultaneous process of a bromination 2,6-and the 1,5-dibromderivatives with increase of contents tetra- and hexabromine content (from 32.5 to 35.9% and from 11.3 to 21.4% respectively).

The analysis of the GC-MS results shows that in the studied conditions it is impossible to insert more than six atoms of bromine into a decalin molecule.

For the solution of this problem, we carried out studying of influence of various initiators of peroxide type on composition of resultants of reaction of a decalin radical bromination. Reaction had been carried out in similar conditions: temperature – 80^0C, time – 24 hours, frequency rate – 3, excess of bromine – 8%; UV-initiation).

The type and amount of peroxide initiator were variables [14]-[16].

When we used azo-*bis*-isobutyronitrile as the initiator with initiator content up to 7% it was impossible to insert more than 10 atoms of bromine in a decalin molecule. We obtained similar results in the presence of H_2O_2 initiation of the process.

However, when we used barium peroxide as the initiator at a temperature of 80^0C, we received the sum of 2 dodecabromine in the amount of 7.3%.

The analysis of GC chromatograms of reaction resultants obtained by GC-MS, even at bromine evaporation not less than 20% from added in the conditions of triple process, shows that it is possible to insert 16 atoms of bromine into a

molecule of decalin. However, their total content in the mix do not exceed 19.9% in mix [17]-[19].

To stabilize bromine radicals the crushed absorber was added to the reaction environment.

5% shall be considered as optimum amount of absorber in reaction 5, increase of which does not lead to essential gain of a perbromdecalin.

The analysis of the experiments proves that optimum conditions of perbromdecalin synthesis are temperature – 80^0C, reaction time – 24 hours, frequency rate of reaction – 3, excess of bromine – 8%; collateral UV- and BaO_2-initiation, in the presence of 5% of an absorber.

In our opinion, it is possible to reach a larger yield of a perbromdecalin by temperature increasing of the process in the specified conditions to 110-120^{0}C. However, process of uncontrollable evaporation of bromine with a partial sintering of reaction mass in laboratory conditions does not allow making it.

To proof effectiveness of the flow diagram of synthesis of a perbromodecalin developed by us, the mass balance of process [20]-[22] was made and the prime cost of a product was calculated on 1 and the 2 loading, at the rate on 1 kg of a perbromodecalin [see in Fig. 1, Tables I-IV]. Material balance equation:

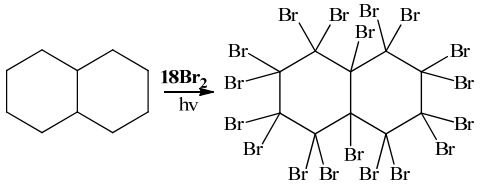

Fig. 1 Perbromination of decaline

TABLE I
REAGENTS RATIO

	$C_{10}H_{18}$
Br_2	6.001 ml:1ml
I_2	29.6089 g:1ml

TABLE II
MASS BALANCE

Statistics of input	Amount, g	Statistics of output	Amount, g
Decalin	138.0	Perbromodecalin	1558.2
Bromine	2876.4	Hydrogen bromide	1456.2
Total	3014.4	Total	3014.4

TABLE III
MASS BALANCE TAKING INTO ACCOUNT EXCESS OF BROMINE (8.33%) AND LOSSES

Statistics of input	Amount, g	Statistics of output	Amount, g
Decalin	138.0	Perbromodecalin	1558.2
Bromine	3116.1	Hydrogen bromide	1456.2
		Loss	239.7
Total	3254.1	Total	3254.1

TABLE IV
MASS BALANCE IN TERMS OF 1 KG OF A PRODUCT

Statistics of input	Amount, g	Statistics of output	Amount, g
Decalin	0.08856	Perbromodecalin	1.0000
Bromine	1.9998	Hydrogen bromide	0.9345
		Loss	0.1538
Total	2.08836	Total	2. 08836

Price will be cut approximately by half considering that after regeneration of bromine about 40% of initial volume of bromine comes back. It follows that at the accounting of regeneration of bromine the price of a product will be reduced by a third of initial cost. Considering the given calculations, prime cost of the perbromdecalin had been received according to the scheme will be 5 times cheaper.

The synthesized bromoderivatives were researched for antibacterial and antifungal activity. Antibacterial activity was researched relating to strains of gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis, Streptococcus agalacticae*, relating to gram-negative strain *Escherichia coli* and to yeast fungus *Candida albicans* using agar diffusion method [23], [24]. The medicines of comparison were gentamicin for bacteria and Nystatin for yeast fungus *Candida albicans.*

The results were statistically processed using 'Statistica 6.0' software package. The obtained results are represented as 'average value ± standard error of an average value'. Inter-group differences were assessed using non-parametric test Mann-Whitney U-test. The reliable values were those at achieved significance point $p<0.05$ [see in Table V].

TABLE V
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF DECALIN BROMODERIVATIVES

Bromo-derivatives	The diameter of growth inhibition zone, mm				
	Sau	Bs	Sag	Ec	Ca
I	9±0.1	7±0.1	11±0.2	12±0.2	4±0.2
II	7±0.1	9±0.1	8±0.2	13±0.2	3±0.1
III	15±0.1	17±0.1	12±0.2	15±0.2	6±0.1
IV	18±0.1	16±0.1	13±0.2	14±0.2	7±0.2
V	22±0.1	18±0.1	16±0.2	13±0.2	7±0.1
VI	23±0.1	22±0.1	18±0.2	14±0.2	9±0.1
VII	19±0.1	20±0.1	13±0.2	17±0.2	6±0.2
VIII	27±0.1	18±0.1	16±0.2	18±0.2	13±0.1
IX	24±0.1	17±0.1	17±0.2	20±0.2	15±0.1
X	26±0.1	21±0.1	18±0.2	22±0.2	17±0.2
XI	29±0.1	29±0.1	14±0.2	24±0.2	18±0.1
XII	31±0.1	27±0.1	19±0.2	26±0.2	19±0.1
XIII	20±0.1	24±0.1	21±0.2	22±0.2	8±0.2
XIV	18±0.1	18±0.1	22±0.2	21±0.2	9±0.1
Gentamicin	26±0.1	24±0.1	23±0.1	23±0.2	-
Nystatin	-	-	-	-	22±0.1

Note. Sau - *Staphylococcus aureus,* Bs - *Bacillus subtilis,* Sag - *Streptococcus agalacticae*, Ec - *Escherichia coli*, Ca - *Candida albicans.* Numbers of decalin bromoderivatives equal to specified above.

As a result of research it is established that the presented samples (VIII, IX-XI) show the expressed activity, in the relation the gram-positive microorganisms (*Staphylococcus aureus*, *Bacillus subtilis*), the expressed activity in the relation

the gram-negative microorganisms (*Pseudomonas aeruginosa*, *Escherichia coli*) showed X-XIV bromoderivatives. X-XII substances showed the expressed antifungal activity to *Candida albicans* yeast fungus.

And the other substances have moderate antibacterial effect to gram-positive, gram-negative microorganisms and weak antifungal activity to *Candida albicans* yeast fungus.

III. Conclusion

1. The main regularities of a decalin radical bromination reaction have been studied for the first time.
2. There are studied the temperature effect and durations of reaction, frequency rate of process and a ratio of initial components, type and amount of the reaction initiator to decalin bromination degree.
3. There are described mass-spectral characteristics for 13 new, earlier not described products of a decalin bromination.
4. There are established antibacterial and antifungal activities of synthesized bromine derivatives.
5. There is developed the technology of perbromdecalin synthesis, structure of which is confirmed by its ^{13}C NMR and mass spectrums.
6. It is experimentally proved that optimum conditions of synthesis are: temperature of reaction - 80^0C, reaction time - 24 hours, frequency rate of reaction - 3, amount of the initiator of BaO_2 - 5%; amount of the stabilizer – an absorber - 5%; surplus of Br_2 - 8.33%.
7. The technological flowchart of synthesis of a perbromo-decalin is developed; the mass balance of process is made.
8. It has been established that decalin bromoderivatives has expressed antibacterial action relating to the gram-positive microorganisms (*Staphylococcus aureus*, *Bacillus subtilis*), the gram-negative microorganisms (*Pseudomonas aeruginosa*, *Escherichia coli*) and antifungal action relating to *Candida albicans* yeast fungus.

Acknowledgment

Authors are grateful to the Foundation the First President of the Republic of Kazakhstan – the Leader of the Nation for award of financial support.

The authors are very much indebted to the Center of Physico-Chemical Methods of Research and Analysis for having provided the equipment where the work has been developed.

References

[1] E. Tsuchida, E. J. G. Riess, P. E. Keipert, *Blood Substitutes*, Lausanne: Elsevier Science SA, 1998.
[2] J. G. Riess, *Biomater. Artif. Cells Immobil. Biotechnol.*, vol. 20, pp. 183-202, 1992.
[3] O. P. Habler, M. S. Kleen, J. W. Hutter, *Transfusion*, vol. 38, pp. 145-155, 1998.
[4] J. L. Kiplinger, T. D. Richmond, *J. Am. Chem. Soc*., vol. 118, no. 7, pp. 1805-1812, 1996.
[5] I. P. Ushakova, N. A. Braghina, A. F. Mironov, *Halogenation methods in organic synthesis*, Moscow: MCTI, 2005.
[6] B. V. Passet, *Main processes chemical synthesis of biologically active substances,* Moscow: Geotar-Media, 2002.
[7] L. N. Milovanova *Manufacturing techniques of dosage forms*, Rostov: Phoenix, 2002.
[8] R. J. Lagow, T. R. Beirschenk, T. J. Juhkle., H. Kawa, *Synthetic fluorine chemistry*, N.Y.: Wiley, 2009.
[9] G. Marchionni, A. Staccione, G. Gregorio, *J. Fluorine Chem.,* vol. 47, pp. 515-518, 2004.
[10] I. L. Knunyants, G. G. Jacobson, *Synthesis of fluororganic compounds,* Moscow: Chemistry, 2000.
[11] B. Gething, C. Patrick, M. Stacey, J. Tatlow, *Nature*, vol. 178, pp. 199-208, 1956.
[12] G. G. Jakobson, V. D. Shteingartz, *Izv. Akad. Nauk, Ser.Khim*., vol. 8, pp. 1551-1558, 1964.
[13] G. Fuller, *J. Chem. Soc*., vol. 111, pp. 6264-6272, 1965.
[14] C.-M. Hu, F. Long, Z.-Q. Xu, *J. Fluorine Chem*., vol. 48, pp. 29-40, 1990.
[15] J. L. Kiplinger, T. D. Richmond, *J. Am. Chem. Soc*., vol. 118, pp. 1805-1812, 1996.
[16] T. Hamatsuka, T. Suzuki, Y. Itoh, H. Hirata, *Chem. Pharm. Bull*., vol. 36, pp. 4225-4231, 1988.
[17] S. Ayabe, *Arch. Biochem. Biophys*., vol. 261, pp. 458-461, 1988.
[18] G. Kochs, S. Pilge, G. Stockmanns, *Eur. J. Biochem*., vol. 155, pp. 311-318, 1986.
[19] E. A. Kean, M. Gutman, T. P. Singer, *Biochem. Biophys. Res. Commun.*, vol. 40, no. 6, pp. 1507-1513, 1970.
[20] C.-L. Peng, S.-W. Chen; Z.-F. Lin, *Prog. Biochem. Biophys*, vol. 27, pp. 658-661, 2000.
[21] W. Heller, K. Hahibrock, *Arch. Biochem. Biophys*., vol. 200, pp. 617-619, 1980.
[22] L. Beerhues, R. Wiermann, *Ztschr. Naturforsch. C*, vol. 40, pp. 160-165, 1985.
[23] M. Lahlou, *Phytother. Res*., vol. 18, pp. 435-448, 2004.
[24] Sh. Inouye, H. Yamaguchi, T. Takizawa, *J. Infect. Chemother.*, vol. 7, no., 4, pp. 251-254, 2001.