



(86) Date de dépôt PCT/PCT Filing Date: 2016/07/08
(87) Date publication PCT/PCT Publication Date: 2017/01/19
(45) Date de délivrance/Issue Date: 2023/09/19
(85) Entrée phase nationale/National Entry: 2018/01/08
(86) N° demande PCT/PCT Application No.: US 2016/041427
(87) N° publication PCT/PCT Publication No.: 2017/011283
(30) Priorité/Priority: 2015/07/15 (US62/192,778)

(51) Cl.Int./Int.Cl. *C07D 295/088* (2006.01)
(72) Inventeurs/Inventors:
PENDERGAST, JOHN G., US;
DIXIT, RAVINDRA S., US;
KING, STEPHEN W., US;
LAROCHÉ, CHRISTOPHE R., US
(73) Propriétaire/Owner:
DOW GLOBAL TECHNOLOGIES LLC, US
(74) Agent: SMART & BIGGAR LP

(54) Titre : PROCÉDE POUR LA PRODUCTION DE COMPOSÉS HYDROXYÉTHYL PIPÉRAZINE
(54) Title: PROCESS FOR MAKING HYDROXYETHYL PIPERAZINE COMPOUNDS

(57) Abrégé/Abstract:

The present invention relates to an improved process for making hydroxyethyl piperazine compounds especially mono-hydroxyethyl piperazine. The improvement comprises reacting piperazine and an alkylene oxide, preferably ethylene oxide in a reactive distillation column.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2017/011283 A1

(43) International Publication Date
19 January 2017 (19.01.2017)

- (51) **International Patent Classification:**
C07D 295/088 (2006.01)
- (21) **International Application Number:**
PCT/US2016/041427
- (22) **International Filing Date:**
8 July 2016 (08.07.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/192,778 15 July 2015 (15.07.2015) US
- (71) **Applicant:** DOW GLOBAL TECHNOLOGIES LLC
[US/US]; 2040 Dow Center, Midland, MI 48674 (US).
- (72) **Inventors:** PENDERGAST, John G.; 2301 N. Brazosport Blvd., Freeport, TX 77541 (US). DIXIT, Ravindra S.; 2301 North Brazosport, Freeport, TX 77541 (US). KING, Stephen W.; 2301 N. Brazosport Blvd, Freeport, TX 77541 (US). LAROCHE, Christophe R.; 2301 N. Brazosport Blvd, B1605 Building, Freeport, TX 77541 (US).
- (74) **Agent:** CHRISTY, M. Robert; The Dow Chemical Company, Intellectual Property, P.O.Box 1967, Midland, Michigan 48641-1967 (US).
- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title:** PROCESS FOR MAKING HYDROXYETHYL PIPERAZINE COMPOUNDS

(57) **Abstract:** The present invention relates to an improved process for making hydroxyethyl piperazine compounds especially mono-hydroxyethyl piperazine. The improvement comprises reacting piperazine and an alkylene oxide, preferably ethylene oxide in a reactive distillation column.



WO 2017/011283 A1

PROCESS FOR MAKING HYDROXYETHYL PIPERAZINE COMPOUNDS

FIELD OF THE INVENTION

5 The present invention relates to an improved process for making hydroxyethyl piperazine compounds especially mono-hydroxyethyl piperazine. Said process relates to ethoxylation of piperazine with an alkylene oxide, preferably ethylene oxide using reactive distillation to increase the yield of mono-hydroxyethyl piperazine over di-hydroxyethyl piperazine.

10

BACKGROUND OF THE INVENTION

 Hydroxyethyl piperazine compounds are generally made by reacting an excess of ethylene oxide with piperazine. One of the difficulties is that, in addition to producing
15 mono-hydroxyethyl piperazine, the ethoxylation of piperazine leads to the formation of di-hydroxyethyl piperazine as a byproduct along with any unreacted ethylene oxide and/or piperazine. Whether a batch or a continuous process is employed, the resulting reaction mixture must be separated by multistep distillation to isolate the desired hydroxyethyl piperazine compound from the by-products, for example see USP 6,013,801.

20 Reactive distillation is well known, for example see, USP 5,368,691, and is generally favored for the case of reacting away an azeotrope and driving a reaction to completion. For example see USP 4,435,595 for the production of methyl acetate, US Patent Application No. 2013/0197266 for the production of ethyl acetate, US Patent Application No. 2013/0310598 for the production of glycolate ester oligomers, US Patent
25 Application No. 2014/03787712 for the alkanolysis of polyether polyols to polyester polyols, and US Patent Application No. 2014/0364655 for producing allyl alcohols.

 It would be desirable to have a process to make hydroxyethyl piperazine compounds which favors the production of mono-hydroxyethyl piperazine and/or eliminates the need for a separate multistep distillation.

30

SUMMARY OF THE INVENTION

The present invention is such a process for producing hydroxyalkyl piperazine compounds, preferably hydroxyethyl piperazine compounds, preferably 1-(2-hydroxyethyl)piperazine, 1,4-bis(2-hydroxyethyl)piperazine, and mixtures thereof, comprising the steps of: i) feeding a feed stream of piperazine at a first location into a reactive distillation column having a top, middle, and a bottom, ii) feeding a feed stream of an alkylene oxide, preferably ethylene oxide, at one or more second location into the reactive distillation column, iii) performing the reaction of piperazine and the alkylene oxide, preferably ethylene oxide, in a reaction zone of the reactive distillation column, iv) removing an overhead stream comprising unreacted piperazine from the top of the reactive distillation column, v) removing a bottoms product containing hydroxyethyl piperazine compounds from the bottom of the reactive distillation column.

In one embodiment of the process disclosed herein above, the first location of the feed stream of piperazine is towards the top of the reactive distillation column and the second location of the feed stream of the alkylene oxide, preferably ethylene oxide, is at a location lower on the reactive distillation column than the first location.

In one embodiment of the processes disclosed herein above, the alkylene oxide, preferably ethylene oxide, feed is fed at multiple locations into the reactive distillation column.

In another embodiment, the processes disclosed herein above further comprises the steps of: vi) passing the removed overhead stream comprising unreacted piperazine through a condenser, vii) condensing the unreacted piperazine from the overhead stream, and viii) recycling the unreacted piperazine back into the reactive distillation column at a third location which is above the second location of the alkylene oxide, preferably ethylene oxide, feed.

In another embodiment, the processes disclosed herein above further comprise the steps of: ix) passing at least a portion of the bottoms product through a reboiler, x) evaporating a portion of the bottoms product, and xi) adding the evaporated portion back to the bottom of the reactive distillation column.

In one embodiment of the processes disclosed herein above, no catalyst is disposed within the reactive distillation column.

In one embodiment of the processes disclosed herein above, one or more catalyst is disposed within the reactive distillation column.

In one embodiment of the processes disclosed herein above, the pressure in the reactive distillation column is equal to or greater than atmospheric pressure.

In one embodiment of the processes disclosed herein above, the reactive distillation column comprises one or more stage.

5 In one embodiment of the processes disclosed herein above, the preferred temperatures of the top, middle, and bottom of the reactive distillation column are: top: 140°C to 160°C, middle: 160°C to 200°C, and bottom: 200°C to 250°C.

BRIEF DESCRIPTION OF THE DRAWINGS

10

FIG. 1 shows a two feed system for producing hydroxyethyl piperazine compounds according to the present invention using a reactive distillation column.

DETAILED DESCRIPTION OF THE INVENTION

15

The object of the present invention is to produce hydroxyalkyl piperazine compounds, preferably hydroxyethyl piperazine compounds, more preferably mono-hydroxyethyl-piperazine, i.e., 1-(2-hydroxyethyl)piperazine, in such a manner as to simplify the purification process. A further objective of the present invention is to improve the yield of mono-hydroxyethyl-piperazine as compared to the amount of di-hydroxyethyl-piperazine, e.g., 1,4-bis(2-hydroxyethyl)piperazine and other by products. Another object of the present invention is that the reaction may be carried out continuously so as to avoid the problems associated with a reaction carried out batchwise.

25 It has now been found that these objectives are reached by reacting an alkylene oxide, for example a C₂ to C₈ alkylene oxide, preferably propylene oxide, more preferably ethylene oxide and piperazine in a reactive distillation process.

In chemical processing, chemical reaction and the purification of the desired products by distillation may be carried out sequentially. The performance of this chemical process structure may be improved by the integration of reaction and distillation in a single multifunctional process unit. This integration concept is called "reactive distillation." As advantages of this integration, chemical equilibrium limitations may be overcome, higher selectivities may be achieved, the heat of reaction may be used in situ for distillation, auxiliary solvents may be avoided, and/or azeotropic and/or closely boiling mixtures may be

more easily separated. Increased process efficiency and reduction in overall capital costs may result from the use of this approach.

A reactive distillation system comprises at least one separator (e.g., a distillation column) comprising a top, middle, and bottom in which the separator, or column, comprises a reaction zone in which a reaction is occurring. In general, suitable separators may include any process equipment suitable for separating at least one inlet stream into a plurality of effluent streams having different compositions, states, temperatures, and/or pressures. For example, the separator may be a column with, or without, a plurality of stages, i.e., trays, packing, or some other type of complex internal structure. Examples of such columns include scrubbers, strippers, absorbers, adsorbers, packed columns, and distillation columns having valve, sieve, or other types of trays. Such columns may employ weirs, downspouts, internal baffles, temperature control elements, and/or pressure control elements. Such columns may also employ some combination of reflux condensers and/or reboilers, including intermediate stage condensers and reboilers. In an embodiment, the reactive distillation system described herein may comprise a distillation tower without any catalyst disposed therein. In another embodiment, the reactive distillation system described herein may comprise a distillation column having at least one catalyst disposed therein.

In one embodiment of the invention, the reactive distillation column has two feeds. Piperazine is fed at a first location which is located towards the upper (or top) part of the column and ethylene oxide is fed at one or more second location which is located towards the lower (or bottom) part of the column. A schematic for a double feed reactive distillation column of the process of the present invention is schematically illustrated in **FIG. 1**. This system includes a reactive distillation column **1** having a reactive zone, a condenser **14**, and a reboiler **15**. In the illustrated system, the piperazine feed **2** is delivered at or near the top of the reactive distillation column **1**, and the ethylene oxide feed **3** is delivered below the piperazine feed **2** at multiple locations, for example **3a**, and/or **3b**, and/or **3c**. Due to boiling point differences of the piperazine and the ethylene oxide, the piperazine moves towards the bottom of the reactive distillation column **1** and the ethylene oxide moves towards the top of the reactive distillation column **1** providing counter current contact between the two. Unreacted piperazine and/or ethylene oxide may move upward exiting the top **4** of the reactive distillation column **1** and the piperazine may be condensed in the condenser **14** for recycle **10** and/or reclamation **12** and ethylene oxide reclaimed or recycled **16**. The hydroxyethyl piperazine reaction product, or bottoms product, moves downward

exiting the bottom **5** of the reactive distillation column **1** and is obtained as products **13** from the reboiler **15**.

Distillate removed at the top of the reactive distillation column **1** is passed through a condenser **14**, and ethylene oxide is separated from lower boiling constituents, i.e.,
5 piperazine. The ethylene oxide may leave the system as an overhead product stream **16**. The condensed lower boiling constituents, or at least some portion thereof, can be cycled back **10** to the reactive distillation column **1** for further reaction and/or separation.

The bottoms product, or portion thereof, may be passed through reboiler **15**, where a portion of the bottoms product is evaporated and added back to the bottom of the reactive
10 distillation column **1**. The remaining bottoms product may pass out of the system as product stream **13**. The product stream **13** comprises the mono-hydroxyethyl piperazine produced in the reactive distillation column **1** along with any side products, i.e., di-hydroxyethyl piperazine, etc., produced by the reaction. The reactive distillation column reflux and reboil ratios are maintained to optimize the amount of mono-hydroxyethyl
15 piperazine in the bottoms product. In an embodiment, the bottoms product stream **13** may comprise greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 85%, greater than 90%, or greater than 95% mono-hydroxyethyl piperazine by weight.

In one embodiment, the piperazine recycle **10** is fed into the reactive distillation column at a third location which is above the second location of the piperazine feed **2**.

20 In one embodiment, the piperazine recycle **10** is fed into the reactive distillation column at a third location which is the same level, e.g., stage, as the first location of the piperazine feed **2**.

In one embodiment, the piperazine recycle **10** is fed into the reactive distillation column at a third location which is below the first location of the piperazine feed **2** but
25 higher than the second location of the ethylene oxide feed **3**.

The reactive distillation column **1** of the process of the present invention may comprise one or more stage. The number of stages is not particularly limited as long as a distillate with unreacted piperazine and ethylene oxide and a bottoms product comprising hydroxyethyl piperazine compounds is produced. Preferably there is one or more stage,
30 more preferably 2 or more stages, more preferably 3 or more stages, and even more preferably 4 or more stages. Preferably there are 30 or less stages, more preferably 20 or less stages, more preferably 15 or less stages, and even more preferably 10 or less stages.

In one embodiment of the process of the present invention, the reactive distillation column does not have any catalyst disposed therein, in other words there is no catalyst disposed within the reactive distillation column.

In one embodiment of the process of the present invention, the reactive distillation column does have one or more catalyst disposed therein, in other words there is one or more catalyst disposed within the reactive distillation column. When a catalyst is present, any suitable ethoxylation catalyst may be used which is known to one skilled in the art. The catalyst may be homogeneous or heterogeneous. A preferred catalyst is a heterogeneous catalyst, for example water, ion exchange resins, zeolites, clays, mixed metal oxides and other solid ethoxylation catalysts known to one skilled in the art.

In one embodiment of the process of the present invention, the reactive distillation column **1** is operated at equal to or greater than atmospheric pressure.

In another embodiment of the process of the present invention, the reactive distillation column **1** is operated at a positive pressure, preferably 1.05 bar absolute, more preferably 1.1 bar absolute, and even more preferably 1.2 bar absolute.

In one embodiment of the process of the present invention, the molar ratio of piperazine feed to ethylene oxide feed is 4 to 1, preferably 3 to 1, preferably 2 to 1, and more preferably 1 to 1.

In one embodiment, the preferred temperatures of the top, middle, and bottom of the reactive distillation column are: top: 140°C to 160°C, middle: 160°C to 200°C, and bottom: 200°C to 250°C.

Preferably, the condenser temperature is from 110°C to 145°C, more preferably 120°C to 130°C, and even more preferably 125°C to 130°C.

25

EXAMPLE

The process of the present invention is simulated numerically using commercially available software, ASPENPLUSTM version 8.6. Physical properties are developed from data regression. The process is numerically simulated by using the rigorous distillation module named RADFRAC within Aspen. This block accommodates both rigorous separation as well as the ability to specify reactions on stages within the tower. These reactions may either be equilibrium reactions or kinetically controlled reactions, as is the case in this application.

A distillation tower provides a means for stage-wise countercurrent contact of liquid proceeding down the tower, with vapor rising up through the device, with the vapor and liquid being brought into intimate contact with the liquid. This may be done with either trays or packing, though in this case, trays are used in the simulation. The absolute units
 5 used in this simulation do not necessarily reflect any commercial reality, but rather reflect a demonstration for the concept and practicality of the concept.

The simulation uses a process configuration as shown in **FIG. 1** and is a representation of the RADFRAC block with piperazine feed provided to the upper section of the tower. Ethylene oxide, shown coming from a common source and then separated into
 10 multiple stream, is fed to stages between the piperazine feed and the bottom of the tower.

Table 1 is a stream table for the process described in **FIG. 1**. In the illustrative embodiment, a 10 stage unit is configured. Stage 1 is the condenser and Stage 10 is the reboiler. Piperazine (PIP) is introduced above stage 5. Ethylene oxide (EO) is introduced below stages 5, 7 and 9. Piperazine is introduced at or near the top of the column and EO is
 15 introduced at or near the bottom of the column. The EO is distributed to lower its concentration to optimize the amount of 1-(2-hydroxyethyl)piperazine (HEP) formed over 1,4-bis(2-hydroxyethyl)piperazine (DIHEP).

Table 1

	PIP-FEED	EO-TOP	EO-MID	EO-BOT	TOP-PROD	BOT-PROD
Mole Flow kmol/hr						
PIP	6.965657	0	0	0	2.320443	0.7814593
HEP	0	0	0	0	0.000195303	3.189589
EO	0	2.594268	1.945701	0	0.00224344	3.59E-09
DIHEP	0	0	0	0	3.65E-08	0.673971
Mole Frac						
PIP	1	0	0	0	0.9989501	0.168236
HEP	0	0	0	0	8.41E-05	0.6866686
EO	0	1	1	0	0.000965798	7.72E-10
DIHEP	0	0	0	0	1.57E-08	0.1450954
Mass Flow kg/hr						
PIP	600	0	0	0	199.8757	67.31247
HEP	0	0	0	0	0.0254264	415.2527
EO	0	114.2857	85.71429	0	0.0988303	1.58E-07
DIHEP	0	0	0	0	6.37E-06	117.4349
Mass Frac						
PIP	1	0	0		0.9993787	0.1121874
HEP	0	0	0		0.000127132	0.6920878

EO	0	1	1		0.000494152	2.63E-10
DIHEP	0	0	0		3.18E-08	0.1957248
Total Flow kmol/hr	6.965657	2.594268	1.945701	0	2.322882	4.645019
Total Flow kg/hr	600	114.2857	85.71429	0	200	600
Total Flow cum/hr	0.662639	0.1315219	0.0986414	0	0.2335851	0.6788775
Temperature °C	100	20	20		147.7994	212.3477

Table 2 shows the result of the reactive distillation by stage in units of kilogram moles per hour. The reactants, PIP and EO are shown as being formed, illustrated by the negative numbers. The products, HEP and DIHEP are shown as being formed by the reaction as the PIP is distributed throughout the tower, and the EO proceeds upward through the tower.

Table 2

Stage	PIP	EO	HEP	DIHEP
1	0	0	0	0
2	-0.07847	-0.07898	0.07796	0.00051
3	-0.17904	-0.18282	0.175263	0.003777
4	-0.57152	-0.60335	0.539694	0.031827
5	-1.59848	-1.8574	1.339548	0.258928
6	-0.35293	-0.42151	0.284341	0.068584
7	-1.07262	-1.37917	0.76608	0.306543
8	-0.01064	-0.01435	0.006919	0.003718
9	-6.39E-05	-0.00015	-2.12E-05	8.50E-05
10	0	0	0	0

10

CLAIMS:

1. A process for producing hydroxyalkyl piperazine compounds, comprising the steps of:
 - i) feeding a feed stream of piperazine at a first location into a reactive distillation column having a top, middle, and a bottom,
 - 5 ii) feeding a feed stream of ethylene oxide at one or more second location into the reactive distillation column,
 - iii) performing the reaction of piperazine and ethylene oxide in a reaction zone of the reactive distillation column,
 - iv) removing an overhead stream comprising unreacted piperazine from the top of the reactive distillation column,
 - 10 v) removing a bottoms product containing hydroxyethyl piperazine compounds from the bottom of the reactive distillation column,wherein the first location of the feed stream of piperazine is towards the top of the reactive distillation column and the second location of the feed stream of ethylene oxide is at a location
15 lower on the reactive distillation column than the first location, and wherein the ethylene oxide feed is fed at multiple locations into the reactive distillation column.
2. The process of Claim 1 further comprising the steps of:
 - vi) passing the removed overhead stream comprising unreacted piperazine through a condenser,
 - 20 vii) condensing the unreacted piperazine from the overhead stream, and
 - viii) recycling the unreacted piperazine back into the reactive distillation column at a third location which is above the second location of the ethylene oxide feed.
3. The process of Claim 1 or Claim 2 further comprising the steps of:
 - 25 ix) passing at least a portion of the bottoms product through a reboiler,
 - x) evaporating a portion of the bottoms product, and
 - xi) adding the evaporated portion back to the bottom of the reactive distillation column.
- 30 4. The process of any one of Claims 1 to 3 wherein the hydroxyalkyl piperazine compounds are hydroxyethyl piperazine compounds.

5. The process of Claim 4 wherein the hydroxyethyl piperazine compounds comprise 1-(2-hydroxyethyl)piperazine (HEP), 1,4-bis(2-hydroxyethyl)piperazine (DIHEP), or mixtures thereof.

6. The process of any one of Claims 1 to 5 wherein no catalyst is disposed within the
5 reactive distillation column.

7. The process of any one of Claims 1 to 5 wherein one or more catalyst is disposed within the reactive distillation column.

8. The process of Claim 7 wherein the one or more catalyst is selected from water, an ion exchange resin, a zeolite, clay, and mixed metal oxides.

9. The process of any one of Claims 1 to 8 wherein the pressure in the reactive distillation
10 column is equal to or greater than atmospheric pressure.

10. The process of any one of Claims 1 to 9 wherein the reactive distillation column comprises one or more stage.

11. The process of any one of Claims 1 to 10 wherein the temperatures of the top, middle,
15 and bottom of the reactive distillation column are: top: 140°C to 160°C, middle: 160°C to 200°C, and bottom: 200°C to 250°C.

FIG. 1