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Maximum Data through a Statistical Design

Response surface experimentation served a dual purpose in the synthesis of, 2,5-dimethylpiperazine . . .

${f N}$ defined optimum conditions

${f V}$ developed a possible reaction mechanism .

CATALYTIC REDUCTIVE AMMONIA-TION of 1,2-propanediol yields a mixture consisting mainly of aliphatic and alicyclic diamines. Chief among the products are 1,2-propanediamine and *cis, trans-* 2,5-dimethylpiperazine. Davison sponge nickel catalyst into a 2-liter, electrically heated rocking autoclave, and hydrogen was admitted to the specified pressure. The temperature was brought up quickly with the aid of a built-in auxiliary heating element

$$CH_{3}.CHOH.CH_{2}OH \xrightarrow{+ NH_{3}}{- H_{2}O}$$

$$[CH_{3}.CHOH.CH_{2}NH_{2}] \xrightarrow{+ NH_{3}}{- H_{2}O} CH_{3}.CHNH_{2}.CH_{2}NH_{2} \qquad (1)$$

$$H$$

$$-2H_{2}O \qquad CH_{3}.CH CH_{2} \qquad -2NH_{3}$$

$$CH_{2}.CH.CH_{3}$$

$$H$$

and vented, the catalyst was removed from the reaction mixture by filtration, and the filtrate was stripped of ammonia and water by distillation through a 3 \times 60 cm. column packed with 1/4inch interlocking saddles and equipped with a dephlegmator. The residual amine mixture was fractionated by distillation through a 0.8×45 cm. The dis-Podbielniak-type column. tillate fractions were redistilled, and the responses were calculated on the basis of the weights of the distillate fractions and titration data. The boiling ranges of the various fractions collected were:

Fraction	B.P., C., 760 Mm. Hg
1,2-Propanediamine	101–125
2,5-Dimethylpiperazine	125–180
1,2-Propanediol	180–190

The large boiling range for 1,2propanediamine results from extensive azeotropism with water, and the response was based entirely on titration.

-Salient Features of the Reaction-

- The most probable mechanism of the cyclization reaction forming 2,5-dimethylpiperazine involves condensation of two molecules of 1-amino-2-propanol.
- Water inhibits formation of 2,5-dimethylpiperazine.
- The functions of ammonia, temperature, and pressure pass through maxima. Excessively high temperature causes thermal degradation, and excessive ammonia favors the formation of 1,2-propanediamine, which is a less efficient intermediate for the formation of 2,5-dimethylpiperazine.
- The optimum reaction conditions for the formation of 2,5dimethylpiperazine are: a mole ratio of 4 to 1 ammonia to 1,2-propanediol, 4 hours at a maximum temperature of about 250° C., anhydrous conditions, and initial hydrogen pressure of 1270 p.s.i.
- The 60 to 70% yield of 2,5-dimethylpiperazine can be increased by recycling 1,2-propanediamine and unreacted 1,2-propanediol.

1-Amino-2-propanol, the postulated intermediate, was detected in only chromatographic amounts, which may be explained by its high degree of reactivity under conditions of reaction.

The object of the present investigation was to examine the effect of several factors on the course of reaction and to determine the conditions favorable toward maximum conversion of 1,2propanediol to 2,5-dimethylpiperazine. These studies were carried out following a technique of statistical design and response surface methodology developed by Box and Wilson (7).

Through this methodology, a great deal of information has been gained from a relatively small number of experiments. In addition to determining the optimum conditions for synthesis of 2,5-dimethylpiperazine, a possible reaction mechanism was deduced.

The literature contains only one reference to the synthesis of 2,5-dimethylpiperazine by reductive ammoniation of 1,2-propanediol. The reaction was described by Sasaki (3) who claimed maximum yields of 76% of theory. Repeating Sasaki's procedure, however, the authors obtained maximum yields of only about 50% of theory.

Experimental Technique

Ammonia (either aqueous or anhydrous liquid ammonia) and 1,2-propanediol were charged along with

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and leveled off to the desired temperature, which was recorded using an ironconstantan thermocouple and Varian G-11 recorder. The reaction time was 4 hours at maximum temperature. After the excess of hydrogen was cooled



Reagents are charged to a bomb . . .



... which is inserted into a rocking autoclave



Hydrogen is introduced to pressure the reaction

Residual amine mixture is separated by distillation



Table	I. Factor Levels fo Series of Trials	or the	First
		Factor	Level
	Factor	- 1	+1
C _{NH} 。	Ammonia, g.	51	153
Т	Temperature, ° C.	230	270
$C_{H_{0}O}$	Water, g.	100	500
P	Initial \mathbf{H}_2 pressure,	500	1200
	p.s.i.		

The large boiling range of the main product 2,5-dimethylpiperazine is explained by the ease of sublimation of the compound. Thus although the boiling point of pure 2,5-dimethylpiperazine is 164° C. (760 mm. of Hg.) the compound begins to sublime at much lower temperature. By paper chromatography, however, this fraction was shown to consist of pure 2,5-dimethylpiperazine.

Experimental Design and Analysis

The effect of four independent variables was considered:

> x_1 , ammonia concentration x_2 , maximum temperature x_3 , water concentration x_4 , initial hydrogen pressure

The levels of the four factors were chosen around a base level which gave a yield of about 30% of theory of 2,5dimethylpiperazine. If the purpose of the investigation had been solely to maximize the yield of 2,5-dimethylpiperazine the base level giving 50% vield corresponding to Sasaki's conditions would have been selected. However, it was believed that by studying the effect of water on the system, useful information on reaction mechanism would be gained. Thus, the base level chosen represented the conditions of best yield from preliminary experiments conducted in the presence of water.

The factor levels for the first series of trials are shown in Table I.

The coding which gives the original factor levels in terms of the standardized levels

$$x_{1} = \frac{C_{\text{NH}_{s}} - 102}{51}$$

$$x_{2} = \frac{T - 250}{20}$$

$$x_{3} = \frac{C_{\text{H}_{2}0} - 300}{200}$$

$$x_{4} = \frac{P - 850}{350}$$
(2)

Other independent variables were kept constant. The amount of 1,2propanediol was held at 1.5 moles; catalyst was 13 grams (dry weight); and time was 4 hours at maximum temperature. The process variables were evaluated on four responses:

- y_1 , % yield 1,2-propanediamine y_2 , % yield 2,5-dimethylpiperazine
- y_3 , unreacted 1,2-propanediol
- y_4 , total recovery

where the percentage yields were based on theory.

The first part of the investigation consisted of sixteen trials of a 2⁴ factorial design. Six replications were made at the center of the design to give an external estimate of experimental error. Data from the center point were later used in calculations comprising the second part of this investigation. The 24 factorial along with the responses is shown in Table II.

A preliminary set of estimates of the parameters of the response function were calculated by the method of least squares. These estimates are shown in Table III along with their standard errors, and the statistically significant effects are denoted.

The significant main effects and interactions are given by the following interpretations.

 Table II.
 2⁴ Factorial Design with Center Point and Four Responses

		Factor	Levels		_	Resp	onses	
$Trial^a$	$x_1,$ NH ₃	${f x_2}, \ {f T}$	$\substack{x_3,\ \mathrm{H}_2\mathrm{O}}$	$egin{array}{c} x_4, \ \mathrm{P} \end{array}$	$y_1,$ PDA	$y_2,$ DMP	$y_3,$ PD	$y_{i},$ R
1	1	- 1	- 1	-1	1.8	58.2	24.7	84.7
2	+1	-1	-1	-1	4.3	23.4	45.5	73.2
3	-1	+1	- 1	- 1	0.4	21.9	8.6	30.9
4	+1	+1	1	-1	0.7	21.8	9.1	31.6
5	1	- 1	+1	-1	0.3	14.3	75.5	90.1
6	+1	- 1	+1	-1	4.5	6.3	86.5	96.3
7	-1	+1	+1	1	0.0	4.5	10.0	14.5
8	+1	+1	+1	-1	1.6	21.8	50.1	73.5
9	$-\tilde{1}$	_ 1	- 1	+1	1.3	46.7	43.3	91.3
10	+1	-1	-1	+1	4.2	53.2	39.7	97.1
11	1	-+-1	-1	+1	1.9	23.7	5.4	31.0
12	+1	+1	- 1	+ 1	0.7	40.3	9.7	50.7
13	-1	-1	+-1	+1	0.0	7.5	78.8	86.3
14	-+- 1	- 1	+1	+1	2.3	13.3	77.8	93.4
15	-1	+ 1	+1	+1	0.8	49.3	21.1	71.2
16.	$+\overline{1}$	+1	+ 1	+1	7.3	20.1	37.8	65.2
17^{b}	ō	Ō	ō	ō	5.0	32.8	45.1	82.8

^a The trials were performed in random order. ^b Average yield of six trials.

1,2-Propanediamine (PDA). The effect of ammonia is positive which is to be expected since the formation of 1,2propanediamine involves the total ammoniation of 1,2-propanediol.

2,5-Dimethylpiperazine (**DMP**). Water has a large negative effect, while ammonia exerts a negative though statistically insignificant effect. Hence, the most probable mechanism of cyclization involves loss of water-reaction between amino and hydroxyl groupsrather than loss of ammonia. Equation 1 shows that the most likely course of reaction would be the condensation of two molecules of 1-amino-2-propanol rather than the condensation of two molecules of 1,2-propanediamine. Another alternative, the reaction of 1,2propanediamine and 1,2-propanediol to form 2,5-dimethylpiperazine would also proceed with dehydration; however, this mechanism is less likely from a kinetic standpoint. Undoubtedly, the three reactions all occur to some extent, but the predominant reaction would involve 1-amino-2-propanol condensation. This hypothesis has been partially verified by experiment. The reductive ammoniation of pure 1amino-2-propanol was carried out and gave 64.6% of theory of 2,5-dimethylpiperazine (compare with the optimum yield for PD conversion, Table IX).

An interesting observation on this reaction was that negligible amounts of high boiling amines and undistillable residue were formed. This means that linear polycondensation does not occur to any great extent. The positive effect of pressure is not fully understood and probably has some kinetic significance.

1,2-Propanediol (PD). The effects of temperature and water on unreacted 1,2-propanediol are according to ex-

 b_{24}

b₃₄

Std. errors

End Uses of Piperazines_

Condensation of piperazines with lower alkylene oxides. fatty acids, and alkyl halides produces surfactants

Linear polyamides obtained by condensing piperazines with dicarboxylic acids show promise as synthetic fibers

Other potential applications for piperazine derivatives include their use as agricultural chemicals, stabilizing agents, and rubber chemicals

pectation. Increase in temperature promotes reaction and decreases unreacted 1,2-propanediol while increase in water inhibits the conversion of 1,2-propanediol, as seen earlier, and thus increases the amount of unreacted 1,2-propanediol. The effect of ammonia is small compared with the other effects, and indicates that excess ammonia tends to retard the rate of conversion of 1,2-propanediol by shifting the equilibrium toward formation of 1,2-propanediamine. Thisretardation effect of excess ammonia immediately suggests the following: The ammoniation of the secondary hydroxyl of 1-amino-2-propanol proceeds at a much slower rate than the condensation of two molecules of 1amino-2-propanol to form 2,5-dimethylpiperazine. Since excess ammonia shifts the equilibrium toward 1,2-propanediamine, this reaction becomes the rate determining step and hence the rate of conversion of 1,2-propanediol.

Recovery. By far the largest effect is that of temperature; recovery decreases with high temperature. This is interpreted as indicative of thermal degradation; forming volatile by-products which are lost through the ordinary

- 0.70

- 0.80

 \pm 1.96

+ 2.74

- 0.50

 ± 1.43

distillation process. Hydrogenation to form volatile hydrocarbons, isopropanol, and isopropylamine occurs to much less extent as seen by the positive effect of hydrogen pressure on recovery. The effects of ammonia and water on recovery are in accordance with the foregcing interpretation of effects.

Interactions. A particularly significant interaction exis's between temperature and water. The effect of water in decreasing the yield of 2,5-dimethylpiperazine, increasing the amount of unreacted 1,2-propanediol, and decreasing recovery is more pronounced at the higher temperatures.

The nonlinearity of the preliminary estimates was shown through statistical analysis of the data. The analysis of variance for DMP response is shown in Table IV. And thus, supplemental trials were needed to separate the quadratic effects b_{ii} from the estimate of the mean. Additional trials were conducted at the center and at eight axial points to form a central composite design (2). The factor levels for the second series of trials are shown in Table Equations 2 were again used for V. coding into the standardized levels.

Table III.	Preliminary Estimates of	Parameters	Were Calculated	by Least Squares
Mean	$\overset{y_1,}{ ext{PDA}}$	$\overset{y_2,}{ ext{DMP}}$	$\stackrel{y_3,}{\operatorname{PD}}$	$\overset{y_4,}{ ext{R}}$
$\mathbf{b}_0^{\mathbf{a}}$	2.01	26.64	38.98	67.56
		MAIN EFFECT	S	
$\begin{array}{c} \mathbf{b}_1 \ (\mathbf{NH}_3\\ \mathbf{b}_2 \ (\mathbf{T})\\ \mathbf{b}_5 \ (\mathbf{H}_2\mathbf{O}\\ \mathbf{b}_4 \ (\mathbf{P}) \end{array}$	$ \begin{array}{c} +1.19^{b} \\ -0.33 \\ +0.09 \\ +0.30 \end{array} $	-1.62 -1.22 -9.51 ^c +5.12 ^c	+ 5.55° -20.00° +15.73° + 0.23	$+ 5.06^{\circ} \\ -21.49^{b} \\ + 6.40^{\circ} \\ + 5.47^{\circ}$
		INTERACTIONS	i	
$b_{12} \\ b_{13} \\ b_{14} \\ b_{23}$	-0.29 + 0.63 + 0.12 + 0.66	+2.19 -0.14 +1.58 +8.01°	+ 2.15 + 2.80 - 3.50 - 4.95 ^b	+ 4.11° + 3.23° - 1.74 + 3.78°

^a This is a biased estimate of the mean when the response surface is nonplanar, since quadratic effects b_{ii} are included within (1). ^b Possibly significant (5% < P < 10%). ^c Statistically significant (P < 5%).

+2.81

+0.29

 ± 1.52

+0.69

+0.19

 ± 0.52

Table IV. Analysis of Variance of Preliminary Estimates of DMP Response

d.f.

MS

Source of Variation

•	MAIN EFFECTS	
\mathbf{b}_1 (NH ₃)	1	41.603
\mathbf{b}_2 (T)	1	23.766
b_3 (H_2O)	1	1445.901ª
b ₄ (P)	1	419.226 ^b

2-FACTOR INTERACTIONS

b ₁₂	1	77.001			
b ₁₃	1	0.303			
b ₁₄	1	40	.323		
b ₂₈	1	1025	.601 ^a		
b ₂₄	1	126.001			
b ₃₄	1	1.380			
Higher order interactions	5	267	2.483^{b} .470		
Experimental error	5	39			
^a Highly significant (P nificant $(1\% < P < 5\%)$).	<	1%).	^b Sig-		

The design matrix for the second series of trials is shown in Table VI along with the yields of 2,5-dimethylpiperazine; the response was of immediate interest.

A complete set of estimates of the least square parameters was then calculated for piperazine yield. These parameters are shown in Table VII with their standard errors. Equation 3 is the fitted second degree polynomial with 15 terms.

 $Y = 39.846 - 1.511 x_1 + 1.284 x_2 -$ $8.739 x_4 + 4.955 x_4 - 6.332 x_1^2 -$ $4.391 x_2^2 + 0.021 x_3^2 - 2.505 x_4^2 +$ $2.194 x_1x_2 - 0.144 x_1x_3 + 1.581 x_1x_4 +$ $8.006 x_2x_3 + 2.806 x_2x_4 + 0.294 x_3x_4$ (3)

Statistical analysis was performed, and the estimate of residual mean square based on 10° of freedom was about five times as great as the estimate of experimental error variance. Entering the table of F-ratio, the level of risk was just below 5% which means that bias owing to the existence of higher order terms was possible. However, since the object of the experiment was not to derive an exact functional relationship, the second degree equation was taken to be an adequate representation of the data for present purposes.

After this article was written, a reviewer pointed out to the authors that the

Table	Table V. Factor Levels for the Second Series of Trials						
		Fε	actor Le	vels			
I	Factor	-1.4	0	+1.4			
$c_{\rm NH_{8}}$	Ammonia, g.	30.6	102.0	173.4			
т	Tempera- ture, ° C.	222.0	250.0	278.0			
$\mathbf{C}_{\mathrm{HeO}}$	Water, g.	20.0	300.0	580.0			
P2	Initial H ₂ pressure, p.s.i.	360.0	850.0	1340.0			

Table VI.	Extra	Trials	Forming	a
Central	Comp	osite	Design	

	Re-				
Trial	$x_1, \\ \mathbf{NH}_3$	${f x_2,\ T}$	$x_3, extsf{H}_2 extsf{O}$	$\overset{x_4,}{\mathrm{P}}$	$y_{2},$ DMP
17 18 19 20 21	$0 \\ -1.4 \\ +1.4 \\ 0 \\ 0$	$0 \\ 0 \\ -1.4 \\ +1.4$	0 0 0 0	0 0 0 0	32.8 31.1 28.1 17.5 49.7
22 23 24 25	0 0 0 0	0 0 0 0	-1.4 + 1.4 0 0 0	$0\\0\\-1.4\\+1.4$	$49.9 \\ 34.2 \\ 31.1 \\ 43.1$

	Table VIII.	Orthogonal Tr	ansformation	
	$(x_1 - 0.2650)$	$(x_2 - 1.0330)$	$(x_{b} - 0.3160)$	$(x_4 - 1.6700)$
X_1	0.5815	-0.7137	0.3787	0.0951
X_2	-0.7813	0.4440	0.2763	0.3407
$X_{\mathfrak{z}}$	0.2034	0.1367	-0.3057	0.9209
X_4	0.0738	0.5242	-0.8292	0.1798

Table IX. Confirmatory Trials and Trials at the Predicted Optimum Conditions

								3	lield
	Canonica	l Variabl	es	O:	riginal Va	riables		Pre-	Experi-
X_1	X_2	X_3	X_4	x_1	x_2	x_{i}	x_4	dicted	mental
0	0	0	0^a	+0.3	+1.0	+0.3	+1.7	43.1	49.0
-0.3	-1.6	-1.0	-2.5^{b}	+1.0	+0.5	-1.5	-0.3	40.8	43.1°
0	0	0	-2.5^{d}	0	+0.3	-1.5	+1.2	59.2	61.2
0	0	0	-2.5^{d}	0	+0.3	-1.5	+1.2	59.2	67.5
^a Cano	nical orig	in. ^b Sa	saki's con	ditions ((3). ° Av	erage yie	eld of 3	trials.	^d Predicted

arc sin transformation might have been more appropriate for the Y values. An analysis of the blocking effect has shown that the error variance is not homogeneous, but is a function of the mean, in which case, the arc sin transformation would indeed be preferable. Furthermore, the difference between blocks may be a major contribution to the lack of fit.

optimum.

The coordinates of the center of the system were calculated by partial differentiation of Equation 3 and solution of the resultant set of linear equations. The coordinates were

$$x_1 = +0.265, x_2 = +1.033, x_3 =$$

 $+0.316, x_4 = +1.670$

with a predicted yield of 43.07%.

The nature of the response surface represented by Equation 3 was elucidated by canonical analysis. Canonical reduction of Equation 3 gave

$$Y - 43.07 = -7.59 X_{1^2} - 6.03 X_{2^2} - 2.16 X_{2^2} + 2.58 X_{2^2}$$
(4)

The canonical form of the fitted equation is readily interpreted. The coefficients of X_1, X_2 , and X_3 are negative; therefore a drop in yield will occur upon moving away from the canonical origin along these axes. The coefficient of X_4 is positive, therefore experiments performed in the direction of X_4 will give an improvement in yield. Geometrically, Equation 4 describes a minimax. The functions of ammonia, temperature, and pressure pass through maxima, the function of water passes through a minimum and the canonical origin represents the stationary point. Since moving in the direction of in-

Since moving in the direction of increased water takes us into regions be-

 Table VII.
 Final Estimates of Least Square Parameters for Yield of 2,5-Dimethylpiperazine

yond the experimental range, confirmatory trials were made at $X_1 = X_2 = X_3 = 0$, $X_4 = -2.5$, which gave essentially anhydrous conditions. The transformation expressing the canonical variables in terms of the original variables and vice versa is given in Table VIII.

Using the transformation given in Table VIII the coordinates of the optimum region in terms of the original variables were $x_1 = 0$, $x_2 = +0.3$, $x_3 = -1.5$, $x_4 = +1.2$, and using the coding Equation 2, the reaction conditions were $C_{NH_3} = 102$ grams, T = 250° C., $C_{H_{2}O} = 0$ gram, P = 1270p.s.i. The predicted yield was 59.2%, and two trials gave 61.2 and 67.5%. Additional confirmatory trials were made at the canonical origin and at the conditions of Sasaki's experiment (3). The results were seen to agree reasonably well with prediction. These results are shown in Table IX.

The optimum would be established more definitely by conducting a designed experiment in the predicted region; however, the authors felt that further adjustments would be more profitably made in the pilot plant.

In practice, by recyling 1,2-propanediamine and unreacted 1,2-propanediol, additional amounts of 2,5-dimethylpiperazine could be obtained so that the over-all conversion was well above 70% of theory.

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