about one half of the polymer solution was added, the mixture became gelatinous and broke up into small lumps. After the addition of the polymer solution was complete (about 45 min.), stirring and refluxing was continued for 2 hr. The mixture was cooled and ethanol was cautiously added after which it was poured into 150 ml. of cold 20% HCl. The polymer was removed by filtration, dissolved in methyl ethyl ketone, and reprecipitated from water. The yield was 20 g., 98%. The infrared spectrum showed complete conversion of carbonyl to hydroxyl. Analysis for hydroxyl content gave 5.86% hydroxyl. Calculated hydroxyl for 33% methyl vinyl ketone composition is 6.01%.

Oxime of styrene–methyl vinyl ketone copolymer. Five g. (.03 mole) of styrene–methyl vinyl ketone copolymer and 5 g. (.071 mole) of hydroxylamine hydrochloride were dissolved in a mixture of 30 ml. of absolute ethanol and 30 ml. of dry pyridine. The mixture was refluxed for 48 hr. and then poured into cold water. The clean white solid amounted to 5.5 g. (96%). The infrared spectrum showed complete conversion of carbonyl to oxime.

Anal. Calcd.: N, 4.77. Found: N, 5.01.

The semicarbazone was prepared by an analogous procedure.

p-[2-(Quinoline-4-carboxylic acid)]polystyrene (II). Five g. (.034 mole) of acetylated polystyrene and 5 g. of isatin (.034 mole) were dissolved in 100 ml. of pyridine and 50 ml. of 30% aqueous potassium hydroxide was added. The dark red solution was refluxed for 3 days after which time it was poured into 250 ml. of methanol. The small amount of insoluble material was removed by filtration leaving a clear, deep red solution. The methanol solution was acidified whereupon a reddish-brown solid precipitated and was removed from the yellow solution by filtration. The solid was dissolved in tetrahydrofuran and reprecipitated from water. There was obtained 7.5 g., 80% yield, of a pale pink solid. A model compound was prepared from isatin and acetophenone. The infrared spectrum showed that these two materials were of similar composition.

Acrylonitrile–methyl vinyl ketone. This copolymer, prepared by mass copolymerization of equimolar quantities of these monomers, was precipitated from methyl ethyl ketone solution in methanol. This was a clear, brittle, glassy material with exceptional adhesive properties.

Reduction of methyl vinyl ketone–acrylonitrile copolymer. The methyl vinyl ketone–acrylonitrile copolymer was reduced in the low pressure hydrogenator with Raney nickel catalyst in tetrahydrofuran solution. The pale yellow solid which was isolated showed hydroxyl, nitrile, and amine groups by infrared. A similar reduction on polyacrylonitrile in dimethylformamide yielded a black, insoluble, amorphous mass.

Softening points. This data was taken on the Fisher-Johns apparatus and reported in Table III. The softening point (range) was measured from initial softening to complete flow of the sample.

Acknowledgment. We wish to express our thanks to Donald Casey for help in the preparative work and to Peter Shapras for his help with infrared spectrometry.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY SECTION MIDWEST RESEARCH INSTITUTE]

An Application of Statistical Design to Organic Synthesis. The Reductive Alkylation of *t*-Butylamine (Leuckart Reaction)

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A series of experiments was designed to simultaneously determine by statistical analysis the effect of five experimental conditions on the yield of *t*-butylmethylamine and *t*-butyldimethylamine in the reductive methylation of *t*-butylamine by the Leuckart procedure. Optimum conditions were determined for the preparation of both amines.

Although tertiary amines are the usual products in the Leuckart reaction of formaldehyde with primary amines in the presence of formic acid,[1] we have observed that *t*-butylamine, treated in this manner, yields significant amounts of the secondary amine, *t*-butylmethylamine. Since we had need of a large amount of this product and there is no satisfactory synthesis reported,[2] we considered it of interest to determine the optimum conditions for its preparation by this method. After consideration of some excellent reviews on the mechanism of the Leuckart reaction,[3] we chose to study the effects of several experimental variables. In a previous study in our laboratories,[4] application of the method of experimental design[5] provided outstanding results in determining ideal conditions for a synthesis problem involving the variation of several experi-

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(1) M. L. Moore, *Org. Reactions*, **V**, 307 (1949).

(2) *t*-Butylmethylamine was prepared in unspecified yield (along with neopentylamine) by the hydrogenation of *t*-butylcarbylamine [P. Sabatier and A. Mailhe, *Compt. rend.*, **144**, 957 (1907)]. This compound was also formed in about 6 per cent yield by the alkylation of *t*-butylamine with methyl iodine [N. Bortnick, *et al.*, *J. Am. Chem. Soc.*, **78**, 4039 (1956)]. Hurwitz [U. S. Patent **2,582,128** (1952)] suggests the possibility of hydrogenating the Schiff base (aldimine) formed on treatment of *t*-butylamine with formaldehyde.

(3) See, for example, (a) E. R. Alexander and R. B. Wildman, *J. Am. Chem. Soc.*, **70**, 1187 (1948); (b) V. J. Webers and W. F. Bruce, *J. Am. Chem. Soc.*, **70**, 1422 (1948); (c) P. A. S. Smith and A. J. MacDonald, *J. Am. Chem. Soc.*, **72**, 1037 (1950); (d) D. S. Noyce and F. W. Bachelor, *J. Am. Chem. Soc.*, **74**, 4577 (1952); (e) E. Staple and E. C. Wagner, *J. Org. Chem.* **14**, 559 (1949); (f) C. B. Pollard and D. C. Young, Jr., *J. Org. Chem.*, **16**, 661 (1951).

(4) Results to be published later.

(5) For a general reference to the method of experimental design, see C. A. Bennett and N. L. Franklin, *Statistical Analyses in Chemistry and the Chemical Industry*, John Wiley & Sons, Inc., New York, (1954).

mental factors. Experimental design permits optimum application of statistical analysis to experimental data and can often be the most efficient method of determining optimum reaction conditions. For this reason we believe that it is ideally suited to many problems in organic synthesis and that it should find ever increasing application in this field. Moreover, the method provides some indication of the reliability of the results. The data provide sufficient information for the calculation of the uncertainty or error inherent in the yield variations. When this uncertainty is compared with the difference which is attributed to a variable under study one may reliably determine the probability that the effect is real.

The effects discussed in this paper were significant at the 95% confidence level, that is, the odds are 20 to 1 that the effects were not due to an unfortunate sampling of data.

After a preliminary run to determine approximate reaction conditions, a series of experiments was designed. These were designed to test the effect of five experimental conditions on the yield of secondary and tertiary amines. The initial block of 16 experiments (a half-replicate of a 2^5 factorial experiment) simultaneously compared high and low values of reaction temperature (50° and 80°), reaction time (4 hr. and 6 hr.), rate of addition of formaldehyde (2 ml./min. and 6 ml./min.), and the concentration of formic acid (2 moles and 3 moles) and formaldehyde (0.75 mole and 1.25 moles). The design and randomization of the experiment are presented in Fig. 1.

TEMPERATURE, °C.				50				80		
REACTION TIME, HR.				4		6		4		6
FORMALDEHYDE RATE OF ADDITION, ML./MIN.				2	6	2	6	2	6	2	6
FORMIC ACID, MOLES	2	FORMALDEHYDE, MOLES	1.25	7			11		16	5	
			0.75		9	12		2			4
	3		1.25		1	3		8			10
			0.75	6			15		14	13	

Fig. 1. The design and randomization of the experiment

The consecutive numbers in Fig. 1 (1 through 16) represent the individual runs and the position of the number in the block readily shows the experimental conditions of that run.

In these experiments, *t*-butylamine was mixed with formic acid at ice water temperature to produce the formate salt. This mixture was heated to the specified temperature and formaldehyde (a 37% formalin solution) was added at a prescribed rate. At the end of the experiment, the reaction mixture was analyzed for *t*-butylmethylamine, *t*-butyldimethylamine, and unreacted *t*-butylamine by rectification of the mixture. As will be seen, this method of analysis was not precise but it was accurate enough for our purposes. The yields based on primary amine (conversions) are presented in Table I.

TABLE I

YIELDS BASED ON PRIMARY AMINE (CONVERSIONS)

Experiment Number	Recovered Primary Amine, %	Secondary Amine, %	Tertiary Amine, %
1	45	43	6
2	43	28	25
3	24	46	22
4	43	23	25
5	18	22	55
6	59	29	7
7	27	38	28
8	17	22	55
9	48	27	18
10	19	21	58
11	29	36	30
12	49	26	22
13	41	27	25
14	43	31	22
15	51	28	19
16	19	21	53

It is of interest to note that in all the runs at 80° the formaldehyde was completely utilized. The yields based on formaldehyde ranged from 95 to 109%. Yields in excess of 100% are, of course, a reflection of the accuracy of the analysis by distillation.

A statistical analysis of the yields (Table I) was performed. Effects were tested for significance at the 95% confidence level and the following conclusions were drawn:

1. Under the conditions chosen for study, reaction time and rate of addition are not significant. 2. Increasing the temperature from 50° to 80° causes an increase in the yield of tertiary amine and a decrease in secondary amine yield. 3. An increase in the amount of formaldehyde (from 0.75 to 1.25 moles) causes an increase in the yield of both amines. 4. A significant interaction between temperature and formaldehyde concentration exists. At the low temperature (50°) an increase in formaldehyde concentration increases the yields of both secondary and tertiary amines. At the higher temperature an increase in formaldehyde increases the yield of tertiary amine but reduces the yield of secondary amine. 5. Although not statistically significant, the effect representing the formic acid–temperature interaction was relatively large. The data indicate that at the high temperature the formic acid concentration has little effect on yields. At the lower temperatures, a high formic acid concentration appears to favor secondary rather than tertiary amines.

Figure 2 is a representation of the expected yield values based upon the assumption that only form-

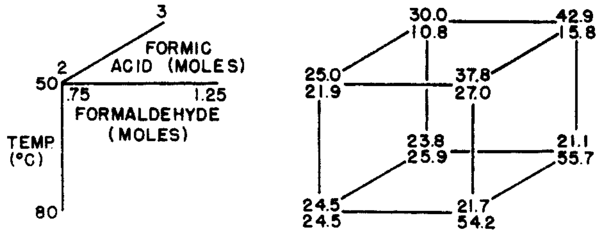

Fig. 2. Expected yield estimates. The yield estimates are based upon a statistical analysis of the experimental data. The upper number represents per cent conversion to secondary amine; the lower number represents per cent conversion to tertiary amine

aldehyde concentration, formic acid level, reaction temperature, and the above-mentioned interactions are important.

Our major objective in these experiments was to find the best conditions for the preparation of the secondary amine. However, it is worth noting that the statistical conclusions and the high ultilization of formaldehyde at 80° both indicate that high yields of the tertiary amine should be formed at high temperatures with excess formaldehyde. Actually, high yields of many tertiary amines have been reported under such conditions but since the reaction of *t*-butylamine had not been reported,[6] one run was made at 90° with excess formaldehyde. The tertiary amine was obtained in almost quantitative (95%) conversion with no detectable amounts of the secondary amine or recovered primary amine.

Our results also indicated that secondary amine formation would be favored by lower reaction temperatures and higher concentrations of formic acid and formaldehyde.

We then designed a series of 24 experiments (a $2^3 \cdot 3$ factorial experiment) to more completely investigate reaction temperatures (46°, 53°, and 60°), high formic acid concentration (3 and 7 moles), high formaldehyde concentrations (1.25 and 2.25 moles), and reaction times (3 hr. and 6 hr.). However, it was found that the reaction did not proceed to any great extent at 46°. It was apparent that the higher levels of formic acid concentration caused a considerable decrease in the reaction rate. This retarding effect of a large excess of formic acid was observed before in reactions of this type.[3e]

The experimental design was changed to eliminate the study at 46° (thus becoming a 2^4 factorial experiment) and the remaining experiments were performed. The design and randomization of this series of experiments was carried out in the same manner as the first block of experiments (Fig. 1). In this series, the reaction conditions varied from those which barely allowed the reaction to proceed to those which permitted fairly extensive reaction. (The yields of carbon dioxide varied widely from 11% to 156%, based on the amount of carbon dioxide required in the formation of the secondary amine.) The effect of high concentrations of formic acid in decreasing reaction rate was especially significant. An increase in formic acid concentration (from 3 to 7 moles) caused a fourfold decrease in the extent of the reaction during 3 hr. at both temperatures and a twofold decrease during the 6-hr. experiments at both temperatures. However, a complete statistical analysis of these experiments was not possible since, under conditions where the reduction had not occurred to a large extent, a considerable quantity of *t*-butylaldimine[7] (a Schiff base) was formed. This seriously interfered with the analysis of the secondary amine because *t*-butyl aldimine boils within a few degrees of the secondary amine and has been shown to be unstable.[8] In all cases, however, the yield of crude secondary amine was no greater than the highest yield found in the first block of experiments.

Thus, the application of statistical design to this reaction has provided a convenient set of experimental conditions for the satisfactory production of the secondary amine. The better runs in the first block of experiments produced the secondary amine in yields as high as 60% with 46% conversion. This is probably very close to the optimum for this reaction since these were the highest yields obtained in a systematic study of the important experimental variables at levels near those which produced these yields.

EXPERIMENTAL[9]

Starting materials. t-Butylamine is commercially available and was used without purification. The formaldehyde used was a formalin solution (38% formaldehyde) and the formic acid used was a technical grade (90% formic acid).

General procedure. t-Butylamine (73 g., 1.0 mole) was cautiously added dropwise (30 min.) to ice cold formic acid (the amount of formic acid was systematically varied between 2 and 7 moles). The flask was equipped with a reflux condenser and a thermometer well, and the contents were stirred with a magnetic stirrer. The reaction mixture was brought to the required temperature by means of a heating mantle and the temperature was maintained within a degree of the desired temperature by means of a capacitance relay attached at the proper position on the thermometer. This "Thermo-Cap Relay" provided an off-on switch for the heating-mantle variac. Formaldehyde solution was added dropwise at a specified rate by means of an apparatus similar to that used for surgical infusions. It consisted of a graduated addition funnel from which the formaldehyde solution was conducted downward through a Tygon tube to a calibrated dripmeter. This dripmeter consisted of a glass tube $1/2 \times 2$ in. which was half filled with the solution. As the solution passed dropwise into the dripmeter, the solution flowed downward to the reaction mixture through another Tygon

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[6] This reaction was subsequently reported by L. Spialter and J. Pappalardo, *J. Org. Chem.*, 22, 840 (1957).

[7] M. D. Hurwitz, U. S. Patent **2,582,128** (1952).

[8] *t*-Alkylamines are unique in their reaction with formaldehyde, since they give excellent yields of *relatively* stable monomeric aldimines. Normally the reaction of aliphatic primary and secondary carbinamines with formaldehyde yields cyclic trimeric azomethines [*Tertiary-Alkyl Primary Amines*, Rohm & Haas Co., Technical Publication No. SP-33, p. 24 (1955)].

[9] All melting points and boiling points are uncorrected.

tube which could be constricted by means of a pinch clamp. The apparatus was adjusted to deliver formalin solution at the prescribed rate and provided a very convenient method of accurately controlling the rate of addition.

The reaction mixture was stirred by means of the magnetic stirrer and held at the specified temperature for the required time. During the entire experiment the evolution of carbon dioxide was followed volumetrically using a "wet-test meter". The reaction mixture was then treated with 50 ml. of concentrated hydrochloric acid and 100 ml. of liquid was distilled from the mixture. The residue was made strongly basic with a 50% solution of sodium hydroxide and this mixture was fractionally distilled through a 3-ft. bubble-cap column which was equipped with a reflux head set at a reflux ratio of ten to one. The yield of secondary and tertiary amine and the amount of recovered primary amine was determined from a plot of the boiling point and refractive index of the distillate.

t-Butyldimethylamine is obtained as an azeotrope with water (86.3% amine, 13.7% water) under these conditions. The composition of the azeotrope (b.p. 76°, d_4^{25} 0.771) was determined by titration, vapor phase chromatography (Perkin-Elmer, Column Material "F"), and density. The pure *t*-butyldimethylamine could be obtained by distillation of the azeotrope from solid sodium hydroxide.

t-Butyldimethylamine. The described general procedure was used. Optimum conditions were: a 4:1 molar ratio of formic acid to amine, a 2.5:1 molar ratio of formaldehyde, a reaction temperature of 90–100°, and a reaction time of 2 hr. These conditions gave a 95% yield of product[6,10] b.p. 89°, n_D^{25} 1.4015, d_4^{25} 0.735, MR_D calcd.: 33.86. Found: 33.49. The melting point of the quaternary ammonium salt, *t*-butyltrimethylammonium iodide, m.p. 225–226° (with decomposition) agrees with the value previously reported.[10]

t-Butylmethylamine. The described general procedure was followed. Experimental conditions which gave the best yield were: A 3:1 molar ratio of formic acid to amine, a 1.25:1 molar ratio of formaldehyde, a reaction temperature of 50°, and a reaction time of 6 hr. The product[10] was obtained in 60% yield and 46% conversion; b.p. 69°, n_D^{25} 1.393, d_4^{25} 0.727, MR_D calcd.: 28.89%. Found: 28.61.

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(10) N. Bortnick, L. S. Luskin, M. D. Hurwitz, W. E. Craig, L. J. Exner, and J. Mirza, *J. Am. Chem. Soc.*, **78**, 4039 (1956).

[CONTRIBUTION FROM INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Studies in Dieckmann Cyclization. I. Cyclization of Triethyl Pentane-1,2,5-tricarboxylate[1]

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Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate has been shown to give diethyl cyclohexanone-2,3-dicarboxylate.

In connection with a research project on the synthesis of diterpenoid resin acids, in progress in this laboratory for some years, it became necessary to undertake the study of the Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate (I).

Dieckmann cyclization of triethyl pentane-1,2,5-tricarboxylate was studied by Perkin and coworkers.[2] It was proved by them that a six-membered ring was formed in preference to a five-membered one, since the product of cyclization on hydrolysis furnished cyclohexanone-3-carboxylic acid. They did not, however, establish whether the intermediate β-keto ester had structure IIa or IIb representing the two possible modes of cyclization.

From a consideration of the inductive effect of substituents in the β-position on an α-methylene group Chakravarti[3] predicted that the cyclization of I should predominantly proceed *via* the route A rather than *via* B or C, resulting in the product IIa. Our results corroborate this view.

Triethyl pentane-1,2,5-tricarboxylate employed in these studies was prepared by two different methods. In the first method ethyl cyclopentanone-2-carboxylate was condensed with ethyl chloroacetate in benzene to produce diethyl cyclopentanone-2-acetate-2-carboxylate which, on being subjected to ring fission with catalytic amount of sodium ethoxide in ethanol, furnished the tri-ester (I). In the second method ethyl chloroacetate was condensed with diethyl sodiomalonate resulting in the formation of diethyl 1-carbethoxysuccinate. The succinic ester derivative was further condensed with ethyl γ-bromobutyrate to yield tetraethyl pentane-1,2,2,5-tetracarboxylate (IV). The tetra-

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[1] Taken from the thesis submitted by Kalyanmay Sen for the degree of Doctor of Philosophy (Science) of the University of Calcutta, April 1957. A preliminary communication on this subject appeared in *Science and Culture,* **19,** 312 (1953).

[2] M. E. Dobson, J. Ferns, and W. H. Perkin, *J. Chem. Soc.,* **95,** 2010 (1909).

[3] R. N. Chakravarti, *J. Chem. Soc.,* 1316 (1953).