616-45-5; 2-pyrrolidinone-*N*-acetic acid, 53934-76-2; *N*-[3-(ethoxycarbonyl)propyl]glycine ethyl ester hydrochloride, 73193-57-4; *N*-(ethoxycarbonyl)-*N*-[3-(ethoxycarbonyl)propyl]glycine ethyl ester, 73193-58-5; 4,*N*-dicarbethoxy-3-piperidinone, 73193-59-6; 2,*N*-dicarbethoxy-3-piperidinone, 73193-60-9; *N*-carbethoxy-3-piperidinol, 73193-61-0; 3-piperidinol hydrochloride, 64051-79-2; *N*-(trifluoroacetyl)-3-piperidinol, 73193-62-1; cyclohexene oxide, 286-20-4; aniline, 62-53-3.

Simplex Optimization of Yields in the Bucherer–Bergs Reaction

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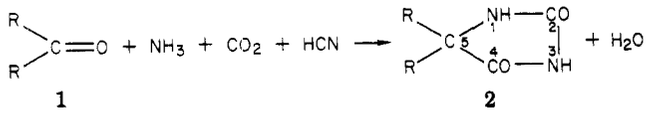
Yields of the spiro-4-thiohydantoins **5** (RR = $(CH_2)_5$) from cyclohexanone and **4** (X = S, Y = O) from adamantanone have been optimized by systematic variation of concentrations of reactants, temperature, time, and solvent composition, as guided by the simplex evolutionary operation. A modification of the original simplex procedure, in which variables for several experiments, rather than for one only, are specified at each step of the procedure, allows optimization to proceed more rapidly.

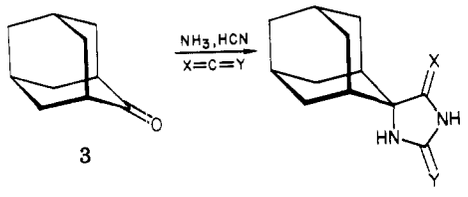
Aldehydes and ketones (**1**) react with ammonia and



1 **2**

hydrogen cyanide to give α-amino nitriles (the Strecker reaction), which may be hydrolyzed to α-amino acids.[1] However, yields with many ketones are poor, and the amino acids are often more conveniently obtained by hydrolysis of hydantoins (**2**), synthesized from ketones by reaction with hydrogen cyanide, ammonia, and carbon dioxide (the latter two in the form of ammonium carbonate). This is the Bucherer–Bergs reaction.[2] Carrington and his colleagues have introduced two variants of this reaction: one employing carbon disulfide in place of carbon dioxide and giving 2,4-dithiohydantoins;[3] the other employing carbonyl sulfide and giving 4-thiohydantoins.[4]

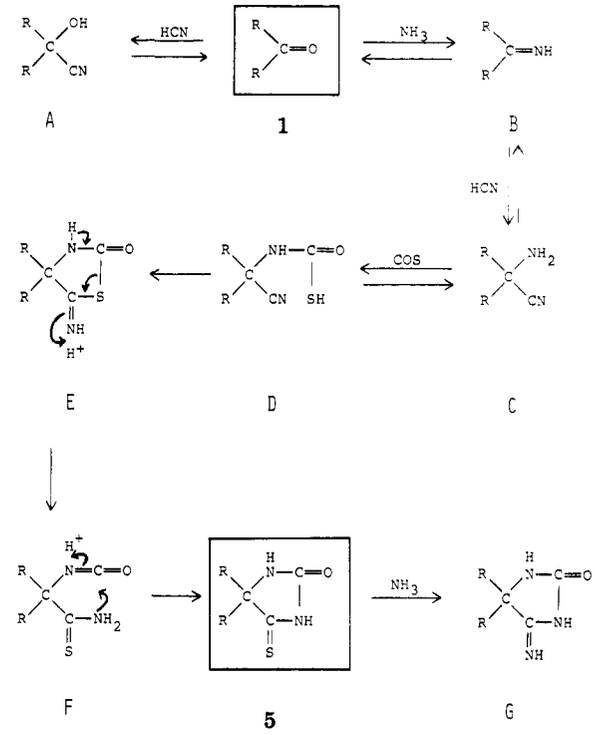
For sterically hindered ketones, even the Bucherer–Bergs reaction sometimes fails unless drastic conditions are used. Thus Nagasawa and co-workers[5] obtained the hydantoin **4** (X = Y = O) from adamantanone (**3**) by the



3 **4**

original (CO_2) procedure only by carrying out the reaction at 120 °C for 3 h in a pressure vessel. Our preliminary studies showed that under less drastic conditions (55 °C at atmospheric pressure) the reaction still took place, but slowly (12% yield of **4**, X = Y = O, after 5 days). Under these conditions Carrington's modified reactions were much faster: with carbon disulfide a 25% yield of **4** (X = Y = S) was obtained after 20 h; and with carbonyl sulfide a 22% yield of **4** (X = S, Y = O) was obtained after 3 h. Since some of the amino acids derived via hydantoins from

Scheme I



hindered ketones have interesting physiological properties,[5,6] we decided to attempt to optimize yields from the modified reaction using carbonyl sulfide.

A possible mechanism for the formation of a 4-thiohydantoin **5** from a ketone **1** is shown in Scheme I.[7,8] The equilibria **1** ⇄ A and **1** ⇄ C have been studied by Commeyras et al.[1] who have shown them to be, as expected, sensitive to pH. The subsequent steps E → F and F → **5** would also be expected to be sensitive to pH. The reaction **5** → G is discussed later.

In carrying out a conventional batchwise preparation of a 4-thiohydantoin, one may expect the yield (based on

(1) Taillades, J.; Commeyras, A. *Tetrahedron* **1974**, *30*, 127, 2493, 3407.
(2) Ware, E. *Chem. Rev.* **1950**, *46*, 403.
(3) Carrington, H. C. *J. Chem. Soc.* **1947**, 681.
(4) Carrington, H. C.; Vasey, C. H.; Waring, W. S. *J. Chem. Soc.* **1959**, 396.
(5) Nagasawa, H. T.; Elberling, J. A.; Shirota, F. N. *J. Med. Chem.* **1973**, *16*, 823.
(6) Christensen, H. N.; Handlogten, M. E.; Lam, I; Tager, H. S.; Zand, R. *J. Biol. Chem.* **1969**, *244*, 1510.
(7) Edward, J. T.; Jitrangsri, C. *Can. J. Chem.* **1975**, *53*, 3339.
(8) Bucherer, H. T.; Lieb, V. A. *J. Prakt. Chem.* **1934**, *141*, 5. Carrington, H. C. *J. Chem. Soc.* **1948**, 619. Edward, J. T. "The Chemistry of Organic Sulfur Compounds"; Meyers, C. Y.; Kharasch, N., Eds.; Pergamon Press: Oxford, 1966; Vol. 2, p 287.

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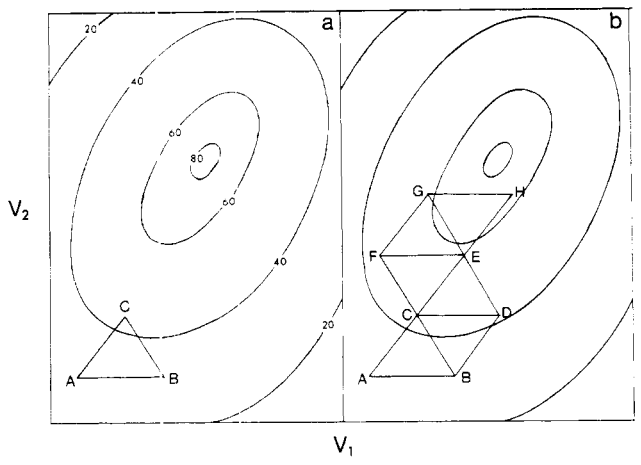

Figure 1. (a) A two-dimensional simplex superimposed on a contour map of iso-response lines (percentage yields shown). (b) Movement of the simplex toward optimum: replacing A by D, B by E, D by F, C by G, and F by H.

ketone) to be affected by at least eight variables: the initial concentrations of ketone, ammonia, hydrogen cyanide, and carbonyl sulfide; the pH; the temperature and time of the reaction; and the solvent. The most usual solvent for the Bucherer–Bergs reaction, in which both organic (ketone) and inorganic (sodium cyanide) reactants are involved, has been 50% aqueous ethanol.[2,4] We have retained this mixed solvent, considering only the ethanol:water ratio as a variable.

For optimization of the yield of such a complicated system, any one-factor-at-a-time approach[9] is unlikely to succeed. The acid–base and other equilibria involving the reactants alter not only their effective concentrations in the reaction mixture but also the pH. The variables are

$$NH_3 + COS \rightleftarrows NH_2COSH \rightleftarrows NH_2COS^- + H^+$$

$$H_2O + COS \rightleftarrows HOCOSH \rightleftarrows HOCOS^- + H^+$$

hence not independent of each other, as required by the method. On the other hand, mapping the response surface of yield vs. variables is impractical: the number of possible combinations of the variables is enormous. Obviously, we need a systematic method which will reduce the immense amount of data that can potentially be accumulated by varying seven or eight variables.

Of the various systematic optimization methods developed by experimental strategists, the simplex method (also called self-directing optimization), first presented by Spendley et al.,[10] is most attractive from a synthetic chemist's point of view, being mathematically simple and easy to implement.[11] It was introduced to analytical chemists by Long in 1969[12] and has attracted considerable attention from analytical and quantum chemists[13] (the latter in search of energy minima), but so far its application to synthetic chemistry has (to our knowledge) not been described.[14] It will undoubtedly become a powerful tool of the synthetic chemist in due time.

Table I. Conditions in Initial $n + 1$ Experiments of the Simplex Method

	variables				
expt	1	2	3 ···	$n-1$	n
1	S_1	S_2	S_3 ···	S_{n-1}	S_n
2	$S_1 + \Delta_1$	S_2	S_3 ···	S_{n-1}	S_n
3	S_1	$S_2 + \Delta_2$	S_3 ···	S_{n-1}	S_n
⋮	⋮	⋮	⋮	⋮	⋮
n	S_1	S_2	S_3 ···	$S_{n-1} + \Delta_{n-1}$	S_n
$n+1$	S_1	S_2	S_3 ···	S_{n-1}	$S_n + \Delta_n$

The method has been well described in a review article for analytical chemists by Deming and Morgan[15] and is only briefly discussed here.

The Simplex Method. A simplex is an n-dimensional figure with $n + 1$ vertices: in two dimensions, a triangle; in three dimensions, a tetrahedron; in n dimensions, a polyhedron of $n + 1$ vertices. This is the probe used to explore the response of a system (in this case, yield of the reaction) to changes in the n variables.

We may illustrate the principles of the method by considering Figure 1, which shows the response (yield) as a function of two variables V_1 and V_2. Our goal is to determine as rapidly as possible the values of V_1 and V_2 which result in the optimum response. The simplex method starts with the three points A, B, and C (chosen at random) of Figure 1a, which form the simplex ABC. The worst point, A, is discarded and replaced by point D (Figure 1b), obtained by reflection of A through the edge BC. The points D, B, and C now define a second simplex, in which the point B is now the worst. Accordingly, it is replaced by E, its reflection through CD, and the new simplex CDE is formed. By repetition of this procedure, the simplex is forced to move toward the optimum by repeated elimination of the worst point, as illustrated in Figure 1b. For the more general case of n variables, $n + 1$ experiments are performed to initiate the optimization process. A convenient way is to assign to each variable a starting value S_i and a step size Δ_i and carry out the $n + 1$ experiments according to the conditions of Table I, although this is not required by the method. The step sizes can be either positive or negative but should not be too small, or else an excessively large number of steps will be required for optimization (see below).

The vertex with the least desirable response is discarded and replaced by its mirror image across the hyperface of the n remaining vertices of the simplex. The variables (V_{new}) of the new point (which define the next experiment to be performed) are obtained by subtracting those of the discarded point from *twice* the average (M) of the retained points:

$$V_{new} = 2M - V_{discard}$$

This move is a *reflection*.

The Modified Simplex Method. The problem of the original simplex method is that step sizes remain the same throughout the optimization process. There is no provision for acceleration when the simplex is far away from the optimum or for refinement when the optimum is near. For these two situations, Nelder and Mead[16] introduced two new operations, *expansion*:

$$V_{new} = 3M - 2V_{discard}$$

(9) Box, G. E. P.; Wilson, K. B. *J. R. Stat. Soc.* **1951**, *B13*, 1.
(10) Spendley, W.; Hext, G. R.; Himsworth, F. R. *Technometrics* **1962**, *4*, 441.
(11) Lowe, C. W. *Trans. Inst. Chem. Eng.* **1964**, *42*, T334.
(12) Long, D. E. *Anal. Chim. Acta* **1969**, *46*, 193.
(13) Dillon, P. W.; Underwood, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 2435, and references cited therein.
(14) C. D. Hendrix, Union Carbide Corporation, South Charleston, WV, in a company report has described the use of the simplex and other strategies for optimizing industrial processes, and A. Commeyras and co-workers (personal communication) have employed it in optimizing conditions for the formation of carbonium ions in superacid solutions. However, we are aware of no published discussion of its application to organic synthesis.
(15) Deming, S. N.; Morgan, S. L. *Anal. Chem.* **1973**, *45*, 278A.
(16) Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308.

Table II. Starting Values and Step Sizes of the Six Variables Using the Modified Simplex Method

variable	cyclohexanone reacn starting value	cyclohexanone reacn step size	adamantanone reacn starting value	adamantanone reacn step size
solvent, % EtOH	50	+25	60	+15
$[NH_3]^a$	4	+2	5	−1
$[COS]^a$	2	−1	2	+1
$[NaCN]^a$	2	+2	1	+1
temperature, °C	53	−10	50	−10
time, h	4	−2	3	+1

[a] Relative to ketone concentration.

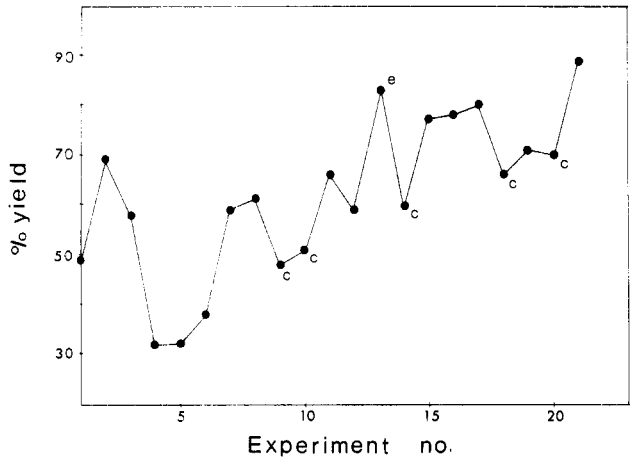

Figure 2. Progress of the sequential simplex toward optimum yield for the 6-variable Bucherer–Bergs reaction of cyclohexanone (c, contraction; e, expansion).

(when the reflected point gives the best response) and *contraction*:

$$V_{new} = 3M/2 - V_{discard}/2$$

(when the reflected point is worse than all the retained points but not as bad as the discarded point) or

$$V_{new} = M/2 + V_{discard}/2$$

(when the reflected point is even worse than the discarded point).

A. Application to Synthesis of 5,5-Pentamethylene-4-thiohydantoin (5, RR = $(CH_2)_5$). The effectiveness of the simplex method was first tested with the relatively cheap ketone cyclohexanone. Carrington and co-workers[4] reported a 49% yield of **5** (RR = $(CH_2)_5$) from this ketone. The concentration of ketone was fixed at 0.3 mol/60 mL of solvent (ethanol–water) and pH was indirectly controlled by the proportions of reactants. The number of variables was thus reduced from eight to six. The reaction was carried out under a reflux condenser, following the Carrington procedure.[4]

The first seven experiments were performed by using the starting values and step sizes of Table II.

Results of the initial seven experiments and of subsequent experiments demanded by the modified simplex procedure are summarized in Figure 2 (full experimental details are given in the Supplementary Material). It can be seen that the yield gradually improved. The best yield after 24 experiments (experiment no. 21) was 88%.

B. Application to Synthesis of Spiro(adamantane-2,4′-imidazolidin)-2′-one-5′-thione (4, X = S; Y = O ≡ 5, RR = $C_{10}H_{14}$). We then proceeded to apply the modified simplex method to the reaction of adamantanone (**3**). The same six variables were investigated, with adamantanone concentration being fixed at 0.2 mol/60 mL of solvent. Starting values and step sizes of the first seven experiments are also given in Table II.

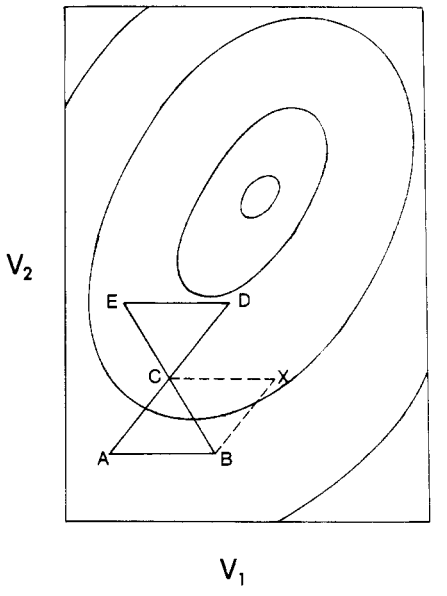

Figure 3. Reflecting both A to D and B to E instead of just A to X.

The yields again increased gradually and reached 76% in experiment no. 24 (the 28th experiment performed). Thereafter yields stabilized at 74 ± 2% until the process was terminated at experiment no. 32 (the 40th experiment performed). Although the number of experiments performed was not impossibly large, the sequential nature of the method made progress slow. Consequently, we decided to investigate a nonsequential variation of the simplex method.

The Multiple-Move Simplex Method. The simplex method and its modifications[17] are all sequential processes: it is always one experiment at a time after the initial (n + 1) experiments. In fact, the conditions with which the (r + 1)th experiment is to be performed will not be known until the rth experiment is completed and its result is compared with other points of the latest simplex. This is not necessarily the best approach to force the simplex to move toward an optimum. Usually, there is more than one obviously bad point in the simplex (especially in the early stages). Hendrix[14] showed that eliminating several points simultaneously is more efficient than eliminating them one by one. This is illustrated in two dimensions in Figure 3.

The optimum number of points to be discarded in a single step is easily determined by a simple calculation and depends on maximizing the gap between the good points (those to be retained) and the bad points (those to be discarded).[14] Suppose responses to the 6 vertices of a simplex are 57, 61, 66, 72, 75, and 80% yield. Table III shows the gaps between bad points and good points divided in five possible different ways. In this case, dividing the points into two groups of three each gives the maximum gap between good points and bad points. Consequently, the three bad points will be discarded simultaneously, each replaced by its mirror image across the hyperface of the three good points. The experimenter will

(17) A modification called the Super Modified Simplex method[18] handles boundary violations better. When the experimenter has reason to believe that the optimum is likely to occur near the physical boundary of a variable, this method is recommended. The disadvantage of the method is its mathematical complexity.

(18) Routh, M. W.; Swartz, P. A.; Denton, M. B. *Anal. Chem.* **1977**, *49*, 1422.

Table III. Gaps between Good Points and Bad Points

57	average of "bad" = 57	57	average
		61	of "bad" = 59
61		66	
66		72	average
72	average	75	of "good" = 73.25
75	of "good" = 70.8	80	
80			difference = 14.25
	difference = 13.8	57	
57		61	average
61	average	66	of "bad" = 64
66	of "bad" = 61.33	72	
72		75	average
75	average	80	of "good" = 77.5
80	of "good" = 75.67		difference = 13.5
	difference = 14.34 (maximum)		
57			
61			
66	average		
72	of "bad" = 66.2		
75			
80	average of "good" = 80 difference = 13.8		

Table IV. Partial Factorial Design for Initializing Four to Seven Variables (Eight Initial Experiments) at Two Levels

	variables						
expt	1	2	3	4	5	6	7
1	low	low	low	low	high	high	high
2	high	low	low	high	high	low	low
3	low	high	low	high	low	high	low
4	high	high	low	low	low	low	high
5	low	low	high	high	low	low	high
6	high	low	high	low	low	high	low
7	low	high	high	low	high	low	low
8	high	high	high	high	high	high	high

now perform three new experiments instead of only one experiment dictated by a sequential method.

The multiple-move method was tested first with the reaction of cyclohexanone and then with that of adamantanone.

A. Application to Cyclohexanone Reaction. The same six variables were investigated. The concentration of ketone remained at 0.3 mol/60 mL of water–ethanol solvent, but the reaction was now conducted in a closed vessel to avoid possible losses of carbonyl sulfide, ammonia, or hydrogen cyanide up the condenser.

Eight initial experiments were carried out by using a different pattern of starting values (Tables IV and V) to show that initial values of the variables need not be chosen according to Table I and that even the number of experiments need not be seven (six plus one). All points except point no. 6 were considered bad and were replaced by new points in the first set of moves. In the second set of moves, 7 points were again discarded. The third and fourth sets of moves discarded two and three points, respectively. A total of 27 experiments was performed and the best yield was 84%. Twenty-four sequential experiments had been required previously to achieve an 88% yield by the modified simplex method; the multiple-move method took only *four* steps and less than *one quarter* of the time. (The results, however, are not strictly comparable because different starting points were used.)

Table V. Starting Values of the Six-Variable Cyclohexanone Reaction (Multiple-Move)

variable	low value	high value
solvent, % EtOH	50	75
$[NH_3]^a$	4	6
$[COS]^a$	1	2
$[NaCN]^a$	2	4
temperature, °C	43	53
time, h	2	4

[a] Relative to ketone concentration.

Table VI. Starting Values and Step Sizes of the Eight-Variable Adamantanone Reaction (Multiple-Move)

variable	starting value	step size	
		series 1	series 2
solvent, % EtOH	60	+10	+20
$[NH_3]^a$	3	+1	+2
$[NH_4Cl]^a$	2	+1	+2
$[COS]^a$	1	+1	+1
$[NaCN]^a$	1	+1	+1
temperature, °C	50	+30	+30
time, h	3	+1	+2
total volume, mL	60	−20	−20

[a] Relative to ketone concentration.

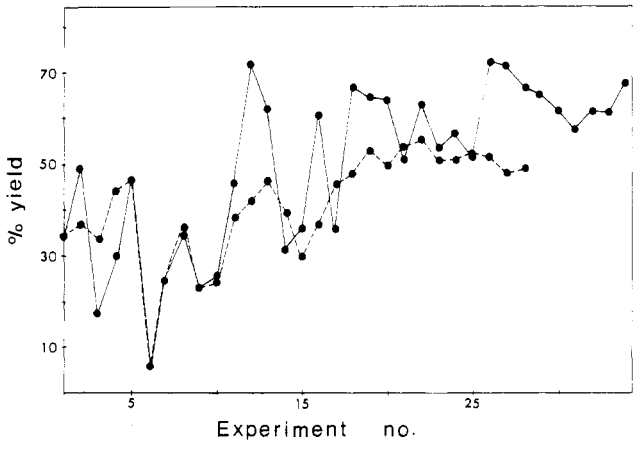

Figure 4. Progress of the multiple-move simplex toward optimum yield for the 8-variable Bucherer–Bergs reaction of adamantanone: broken line, first series of runs; solid line, second series of runs.

B. Application to the Adamantanone Reaction. Finally, the multiple-move simplex method was applied to the reaction of adamantanone, with eight variables: the concentration of ammonium chloride, as well as aqueous ammonia, became a variable, to control pH, its value also being expressed relative to that of the ketone. The ketone concentration was varied by changing the total volume of solvent.

Two series of runs were conducted, having the values of the variables initially chosen as shown in Table VI. The starting values for the two series were the same, but the second had bigger step sizes for some variables. The results after five sets of moves in each series are shown in Figure 4. The yields never exceeded 56% in series 1, but in series 2 yields reached 73%, comparable with those achieved in the sequential method. The time elapsed, however, was one-fifth of that in the sequential method, in spite of the increase in the number of variables. This shows the efficiency of the multiple-move simplex method as well as the great importance of choosing sufficiently large step sizes.

Scientific Feedback. The simplex method derives its strength from the fact that it is directed entirely by

"empirical feedback"[19] and is simple to operate. Box and Draper[19] point out the desirability of using one's understanding of a reaction mechanism ("scientific feedback") as an input in the optimization process. The complexity of the reaction makes this difficult in the present case.

The most remarkable finding is the profound effect of cyanide concentration on yield. The stoichiometry of the reaction demands 1 mol of sodium cyanide/mol of ketone, but the instinct of the organic chemist is to double the mole ratio of such a cheap reagent. However, with cyclohexanone this resulted in a lowered yield of the 4-thiohydantoin, and with adamantanone the yield dropped almost to zero. The simplex methods consistently demanded a mole ratio of sodium cyanide close to the theoretical value. We have no convincing explanation of this finding. An increase in cyanide concentration should result not only in more rapid formation of the cyanohydrin A[1] (Scheme I), which has been isolated as a byproduct, but also in more rapid formation of the amino nitrile C, and these effects might be expected to cancel out. The rates of the reactions linking **1** and **5** in Scheme I probably each have pH optima, with a pH optimum for the overall rate. It accordingly seemed possible that excess sodium cyanide resulted in too alkaline a reaction medium; however, the use of ammonium chloride/ammonia in place of ammonia alone did not lead to striking improvements. These results point to the possibility of the 4-thiohydantoin **5** being degraded by reaction with excess cyanide ion, and indeed such a reaction takes place, but too slowly to account for a large decrease in yield. The products of this degradation have not yet been identified.

The yield of the 4-thiohydantoin from adamantanone leveled off at about 76%, while unreacted cyanohydrin A and amino nitrile C (Scheme I) were still present. Lengthening the reaction time from 3 to 5 h (again, an instinctive response of the organic chemist) caused the yield to drop, presumably because the additional 4-thiohydantoin **5** formed was less than the amount degraded to the imino compound G.

This reaction **5** → G takes place fairly quickly with the spiro-4-thiohydantoin derived from cyclohexanone, but more slowly with that derived from adamantanone; a similar reaction with 2,4-dithiohydantoins has been described by Carrington.[20] This reaction may be expected to become important if the overall reaction **1** → **5** becomes slow because the carbonyl sulfide has been largely lost by hydrolysis.[21]

$$COS + H_2O \rightarrow CO_2 + H_2S$$

Experimental results seem to support these arguments. A reaction that gave a 72% yield of 4-thiohydantoin from adamantanone after 3 h gave a 67% yield after 5 h under the same conditions. However, when the reaction was again run under similar conditions for 5 h, except that more carbonyl sulfide was added at the end of the third hour, an 81% yield of 4-thiohydantoin was obtained; when carbonyl sulfide was bubbled in continuously from the start of the reaction, the yield rose to 83%.

These results illustrate the value of "scientific feedback" in optimizing yields.

The present work demonstrates the value of the multiple-move simplex method for optimizing yields. However, it is possible that the results might have been achieved more economically by starting with fewer initial variables (i.e., without altering solvent composition), because it is always possible to continue a simplex search after increasing the number of variables, but not after decreasing it.[11]

Experimental Section

Melting points are uncorrected. IR spectra were run on samples in Nujol with a Perkin-Elmer 297 instrument. NMR spectra were recorded at 60 MHz and are reported in δ units relative to Me_4Si as an internal standard.

Bucherer–Bergs Reaction of Adamantanone (3). Carbonyl sulfide was bubbled through a cooled solution of concentrated ammonia (8.0 mL) and sodium cyanide (1.42 g) in ethanol (38 mL)/water (14 mL) until a weight of 2.7 g had been absorbed. Adamantanone (3.0 g, 0.02 mol) was added, and the reaction mixture was stirred under reflux at 56 °C for 3.22 h. It was cooled and acidified by dropwise addition of concentrated hydrochloric acid, and the precipitated spiro(adamantane-2,4′-imidazoline)-2′-one-5′-thione (**4**, X = S; Y = O ≡ **5**, RR = $C_{10}H_{14}$) (1.1 g, 23%) was removed by filtration and washed with water. The acidic filtrate was concentrated under reduced pressure and then diluted with water. The precipitated solid S contained more **5** (RR = $C_{10}H_{14}$) together with 2-cyano-2-hydroxyadamantane (A, RR = $C_{10}H_{14}$); the filtrate F contained soluble hydrochlorides of 2-amino-2-cyanoadamantane (C, RR = $C_{10}H_{14}$) and the imino compound G (RR = $C_{10}H_{14}$).

S was extracted with 30 mL of hot petroleum ether (bp 80–100 °C). A small insoluble residue (0.09, g, 2%) of **5** (RR = $C_{10}H_{14}$) was removed by filtration. The soluble material, after evaporation of the solvent, was dissolved in dichloromethane and chromatographed over Florisil. It was recrystallized from petroleum ether (bp 80–100 °C) to yield 0.45 g (13%) of A (RR = $C_{10}H_{14}$): mp (sealed tube) 218–220 °C (lit.[22] mp 206 °C); IR 3400 (OH), 2240 (C≡N) cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.4 (m, 14 H), 3.5 (s, 1 H, OH). Compound A was identical with an authentic specimen prepared according to Stetter and Tillmanns.[22] The combined crops of **5** (RR = $C_{10}H_{14}$) crystallized from ethanol as yellow platelets: mp 269–271 °C; IR 3200, 3100 (NH), 1740 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 1.4–2.4 (m, 12 H), 3.4 (d, 2 H, J = 36 Hz), 8.9 (s, 1 H, NH), 12.3 (s, 1 H, NH).

Anal. Calcd for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.84; N, 11.86; S, 13.57. Found: C, 61.25; H, 7.15; N, 11.71; S, 13.26.

Addition of concentrated ammonia to F gave a precipitate, most of which dissolved in ethanol leaving a residue (0.06 g, 1%) of the imine G (RR = $C_{10}H_{14}$), mp 327 °C, identical (IR, NMR) with a sample prepared below. Removal of the ethanol left 0.6 g (17%) of amino nitrile C (RR = $C_{10}H_{14}$), mp 193–195 °C. It was converted to the *p*-toluenesulfonate salt by treatment with excess *p*-toluenesulfonic acid in ethanol. The salt was recrystallized from dichloromethane–petroleum ether (bp 30–60 °C), mp 180 °C, and was identical (IR, NMR) with material prepared below.

2-Amino-2-cyanoadamantane (C, RR = $C_{10}H_{14}$). A solution of 3.0 g (0.02 mol) of adamantanone, 0.98 g of sodium cyanide, 2.14 g of ammonium chloride, and 4 mL of concentrated ammonia in 36 mL of ethanol/20 mL of water was stirred at 50 °C for 5 h. The solution was cooled, acidified with concentrated hydrochloric acid, and concentrated; 0.20 g (6%) of 2-cyano-2-hydroxyadamantane separated. When the acidic filtrate was made basic, 2.7 g (77%) of 2-amino-2-cyanoadamantane separated: mp 186–190 °C; IR 3380, 3310 (NH), 2210 (C≡N) cm^{-1}; NMR (Me_2SOd_6) δ 1.4–2.35 (m, 14 H), 2.5 (s, 2 H, NH_2). The *p*-toluenesulfonate salt was recrystallized from water: 3.65 g (53%); mp 176–179 °C dec, raised to 180–181 °C after recrystallization from methylene chloride–petroleum ether (1:1); NMR ($CDCl_3$) δ 1.4–2.2 (m, 14 H), 2.4 (s, 3 H, CH_3), 7.1 (d, 2 H, J = 36 Hz), 7.8 (d, 2 H, J = 36 Hz), 8.9 (s, 3 H, NH_3^+).

Anal. Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.03; H, 6.94; N, 8.04. Found: C, 62.14; H, 7.09; N, 8.08.

5-Iminospiro(cyclohexane-4-imidazolidin)-2-one (G, RR = $(CH_2)_5$). 5,5-Pentamethylene-4-thiohydantoin (**5**, RR = $(CH_2)_5$) (2.0 g)[4] was warmed for 2 h to 80 °C in 10 mL of concentrated

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ammonia and 10 mL of water. The solution on cooling deposited 1.8 g (87%) of colorless crystals of the imine G (RR = $(CH_2)_5$): mp 294–295 °C, raised by recrystallization from ethanol–water to 300–301 °C; IR 1700 (C=O), 1670 (C=N) cm^{-1}; NMR (TFA) δ 0.6–1.7 (m, 14 H), 7.7 (s, 1 H, NH), 8.7 (s, 1 H, NH), 9.0 (s, 1 H, NH).

Anal. Calcd for $C_8H_{13}N_3O \cdot 0.5EtOH$: C, 56.83; H, 8.48. Found: C, 56.52; H, 8.45.

The same compound was isolated from a reaction mixture from which 5,5-pentamethylene-4-thiohydantoin (**5**, RR = $(CH_2)_5$) had been isolated in 49% yield, following the procedure of Carrington et al.[4] The acidic filtrate was made basic with concentrated aqueous ammonia, and a 14% yield of G (RR = $(CH_2)_5$) was obtained.

5′-Iminospiro(adamantane-2,4′-imidazolidin)-2′-one (G, RR = $C_{10}H_{14}$). The 4-thiohydantoin **5** (RR = $C_{10}H_{14}$) (2.0 g) was heated at 80–90 °C under reflux with 20 mL of concentrated ammonia, 20 mL of water, and 20 mL of ethanol for 3 h with stirring. The mixture was cooled and filtered, and the solid residue was washed with water and then extracted with dilute hydrochloric acid. The acidic solution was made basic with ammonia and 1.04 g (56%) of colorless crystals of the imine (G, RR = $C_{10}H_{14}$) separated: mp 327 °C (eff); IR 3410, 3150 (NH), 1700 (C=O), 1635 (C=N) cm^{-1}; NMR (TFA) δ 1.6–2.8 (m, 14 H), 8.65 (s, 1 H, NH), 8.8 (s, 1 H, NH), 9.8 (s, 1 H, NH).

Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.72; H, 7.82; N, 19.16. Found: C, 66.03; H, 7.93; N, 19.17.

The acid-insoluble material consisted of 0.65 g (32%) of unreacted starting material.

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Note Added in Proof. It has just come to our attention that simplex and other optimization procedures have been applied by Carlson et al.[23] to the synthesis of enamines from methyl ketones.

Registry No. 3, 700-58-3; **5** (RR = $C_{10}H_{14}$), 73367-52-9; **5** (RR = $(CH_2)_5$), 23000-17-1; A (RR = $C_{10}H_{14}$), 24779-92-8; C (RR = $C_{10}H_{14}$), 24779-93-9; C (RR = $C_{10}H_{14}$) *p*-toluenesulfonate, 73367-53-0; G (RR = $C_{10}H_{14}$), 73367-54-1; G (RR = $(CH_2)_5$), 73367-55-2.

Supplementary Material Available: Conditions and yields for 52 experiments involving cyclohexanone and 112 experiments involving adamantanone (13 pages). Ordering information is given on any current masthead page.

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Photoalkylation of *s*-Triazolo[4,3-*b*]pyridazine with Alcohols and Glycols[1a]

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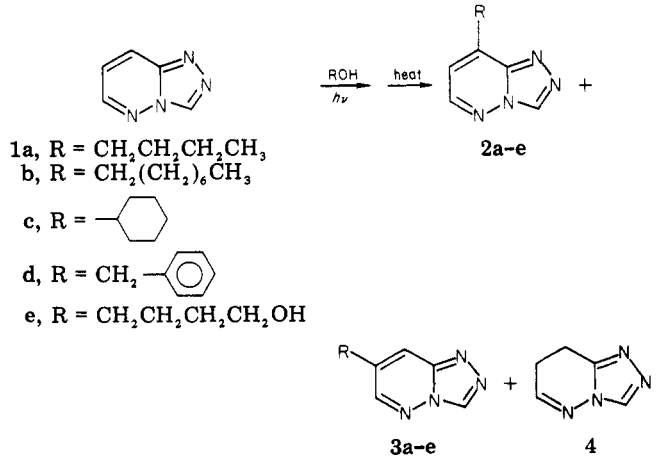
s-Triazolo[4,3-*b*]pyridazine (**1**) was irradiated in 1-butanol to yield 8- and 7-(1′-hydroxybutyl)-7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazines (**5** and **6**) which were isolated and characterized. When this mixture was heated to 260 °C, 8- and 7-*n*-butyl-*s*-triazolo[4,3-*b*]pyridazines (**2a** and **3a**) were isolated. Similar 8- and 7-alkylated compounds were prepared from the photoalkylation of **1** with 1-octanol (**2b** and **3b**), cyclohexanol (**2c** and **3c**), benzyl alcohol (**2d** and **3d**), and 1,4-butanediol (**2e** and **3e**). 7,8-Dihydro-*s*-triazolo[4,3-*b*]pyridazine (**4**) was also isolated from the reaction mixture of the irradiation of **1** with cyclohexanol and with benzyl alcohol. 8-*n*-Butyl-7-methyl- and 7,8-di-*n*-butyl-*s*-triazolo[4,3-*b*]pyridazines (**7** and **8**) have also been prepared. When **2e** or a mixture of **2e** and **3e** was irradiated for 4 h and the reaction mixture heated, 7,8,9,10-tetrahydro-*s*-triazolo[3,4-*a*]phthalazine (**9**) was the only product isolated. Compound **9** was also prepared by an independent synthesis.

The photoalkylation of N-heterocyclic aromatic compounds has been recently treated in reviews by Padwa[1b] and Carnelisse.[2] Photochemical substitutions in purines and purine nucleosides have been reviewed,[3] and the photoinduced methylation of pyrimidines and condensed pyrimidine compounds in acidified methanol has been studied in detail.[4] The photoalkylation of pyridazine in acidified methanol to yield 4-methyl-, 5-methyl-, and 4,5-dimethylpyridazines has been reported by Tsuchiya and co-workers.[5] In addition to using alcohols, other workers have shown that photoalkylation reactions also take place in carboxylic acids,[6] ethers,[7] hydrocarbons,[8] and amines.[9]

Scheme I. Photoalkylation Products



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