The Mechanism of the Alkoxide-Induced Conversion of N-Nitroso-N-alkylamine Derivatives to Diazoalkanes[1]

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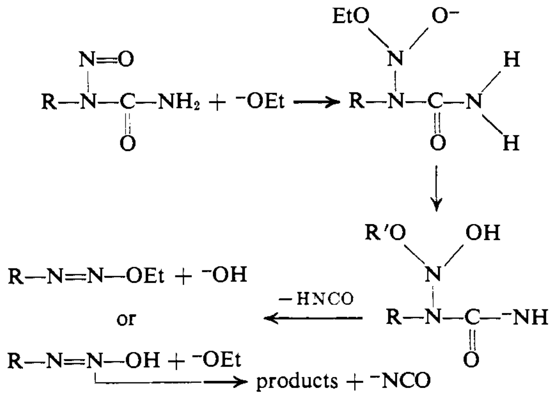
Abstract: The mechanism of the base-induced conversion of N-nitroso-N-(2,2-diphenylcyclopropyl)urea to 2,2-diphenyldiazocyclopropane in ether has recently been shown to differ from the classical mechanism involving base attack on the carbonyl carbon atom of nitrosoalkylamine derivatives. An alternate mechanism involving attack of the base on the nitroso nitrogen atom was postulated. The generality of this mechanism has now been explored. It has been found that all N-nitroso-N-alkylureas investigated show the same behavior (essentially exclusive attack of the base on the nitroso group), regardless of the base (limited to alkoxides), the alkyl group, or the solvent. On the other hand, N-nitroso-N-alkylurethans and N-nitroso-N-alkylamides appear to undergo competitive reaction at the nitroso nitrogen and the carbonyl carbon. This competition is sensitive to the alkyl group, the group attached to the carbonyl carbon atom, the solvent, and the nature of the base. The results of a fairly thorough study to determine the optimum conditions for the synthesis of phenyldiazomethane from N-nitroso-N-benzylamine precursors are also reported.

As the result of a recent study[3] of the mechanism of the reaction of N-nitroso-N-(2,2-diphenylcyclopropyl)urea with base, we concluded that this reaction does not proceed by attack of base on the carbonyl carbon[4] but, instead, goes by attack on the nitroso nitrogen followed by the transformations outlined in Scheme I.

Scheme I



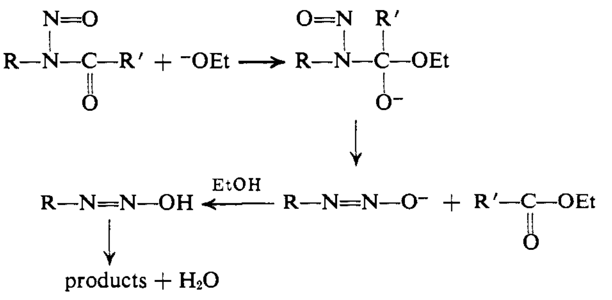
The difference in the path of this reaction and that which apparently obtains in the reaction of potassium carbonate in methanol with nitrosourethans[5,6] and amides[7] (base attack at the carbonyl carbon, see Discussion) prompted us to undertake a systematic investigation of the reaction of nitrosoalkylamine derivatives with base to determine what factors control the course of the reaction. The purpose of this paper is to report the results of these investigations.

Results and Discussion

The results of these investigations are summarized in Tables I–III. Examination of these results reveals certain interesting generalities. In the first place, in all of the ureas studied (Table I) and under all conditions employed, no detectable ethyl carbamate was formed. Thus, the reaction apparently proceeds by attack of the base at some point other than the carbonyl carbon. By analogy with the 2,2-diphenylcyclopropyl system in ether[3] the point of attack is most likely the nitroso nitrogen and although we have not studied these reactions in as much detail as the diphenylcyclopropyl system, they probably all proceed by essentially the mechanism outlined in Scheme I.

In the cases of the N-nitroso-N-alkylurethans and -amides (Tables II and III), the data indicate from 7–90% attack of the base at the carbonyl carbon. That portion of the reaction that proceeds by this path should give the corresponding carbonate or ester and diazotate (Scheme II) which, with the exception of the cyclopropyl system, could react further by the Gutsche and Johnson[5] mechanism to give the diazoalkane and, at least in the benzyl case, carbonium ion products.

Scheme II



$R' = OEt, C_6H_5, CH_3$

Consistent with this mechanism is the fact that the per cent of conversion of 2,2-diphenylcyclopropyl derivatives to decomposition products of 2,2-diphenyldiazocyclopropane (measured by nitrogen evolution) drops off with increasing diethyl carbonate (Table II) and ethyl benzoate (Table III). This would be predicted by the above mechanism since 2,2-diphenylcyclo-

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(1) Based upon a dissertation submitted by Darrel L. Muck to the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Alfred P. Sloan Fellow, 1963–1967.

(3) W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *J. Am. Chem. Soc.*, **88**, 68 (1966).

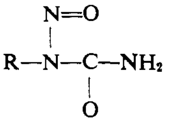
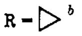
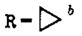
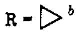
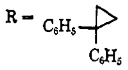
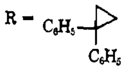
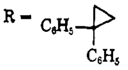
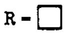
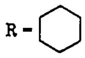
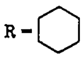
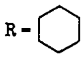
(4) For lead references on the history of this type of reaction, see ref 3. For a very recent discussion of the latter stages of this mechanism, see R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).

(5) *Cf.* C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

(6) F. W. Bollinger, F. N. Hayes, and S. Siegel, *ibid.*, **72**, 5592 (1950).

(7) R. Huisgen and J. Reinertshofer, *Ann.*, **575**, 174 (1952).

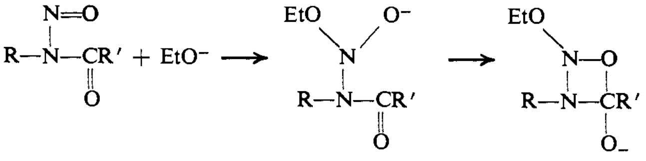
Table I.[a] Decomposition of N-Nitroso-N-alkylureas

Entry	 $R{-}N(N{=}O){-}C({=}O){-}NH_2$	Solvent	Base	Gas evolution, %	Lithium cyanate, %	Ethyl carbamate,[f] %
1	 [b]	Et_2O	LiOEt	71	69	<2
2	 [b]	EtOH	LiOEt	92	87	<2
3	 [b]	EtOH	K_2CO_3	94	. . .	<2
4		Et_2O	LiOEt	75	76	<2
5		EtOH	LiOEt	96	91	<2
6		EtOH	K_2CO_3	95	. .	<2
7		Et_2O[c]	LiOEt	78	65	<2
8		Et_2O	LiOEt	100	88	<2
9		EtOH	LiOEt	100	86	<2
10		EtOH	K_2CO_3	96	. .	<2
11	$R{-}C_6H_5CH_2$ [d]	Et_2O	LiOEt	54[e]	92	<2
12	$R{-}C_6H_5CH_2$ [d]	EtOH	LiOEt	46[e]	83	<2
13	$R{-}C_6H_5CH_2$ [d]	EtOH	K_2CO_3	49[e]	. .	<2

[a] All reactions were run at 0°. Random duplicate runs showed insignificant deviation. [b] The formation of diazocyclopropane was substantiated by effecting the reaction in diethyl fumarate and isolating the pyrazoline (as its N-benzoyl derivative). [c] The LiOEt was dissolved in 2 ml of ethanol before addition so that the reaction conditions would be identical with those employed by Applequist and McGreer.[16] [d] The presence of phenyldiazomethane was shown by allowing it to react with benzaldehyde to give desoxybenzoin. [e] Nitrogen evolution exclusive of phenyldiazomethane decomposition. Upon addition of benzaldehyde, the phenyldiazomethane was decomposed to lead ultimately to essentially quantitative nitrogen evolution. [f] Ethyl carbamate is stable to the reaction conditions.

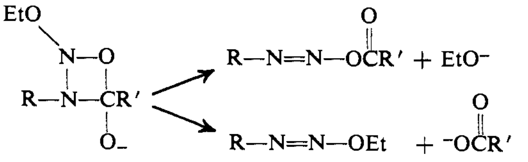
propyldiazotates have been found[3,8] to be stable to the conditions of the reactions under consideration.

The results in Tables II and III also indicate that despite the rather wide variation in the per cent of reaction that goes by attack of the base at the carbonyl carbon, the formation of diazoalkanes and carbonium ion products seems to be little affected (except in the 2,2-diphenylcyclopropyl case—see above). In fact, in the case of the N-nitroso-N-benzylamine derivatives, not only is the total amount of reaction invariant but the ratio of carbonium ion products (predominantly benzyl ethyl ether) to phenyldiazomethane remained surprisingly constant. These results suggest a second route to a species that is structurally similar to a diazotate (or diazo hydroxide). To explain this as well as the formation of alkali carboxylates from the nitrosoamides, we suggest competitive attack of the base on the carbonyl carbon and on the nitroso nitrogen in a manner analogous to the mechanism for the reaction of N-nitroso-N-alkylureas with ethoxide.[9] However, the second stage of the reaction must follow a different path from that proposed for the nitrosourea and for this we suggest a path through a cyclic intermediate analogous to the presumed intermediate for the thermal decomposition of this type of compound.[10]



$R' = OEt, C_6H_5, CH_3$

Collapse of this intermediate could proceed in two different ways, the one leading to the diazo ester and ethoxide and the other leading to the diazo ether and the carboxylate anion. Either of these intermediates could give the observed products.[3] However, of these



two possibilities, the latter is favored for the following reasons. First, the carboxylate would be expected to be more readily displaced than the ethoxide. Second,

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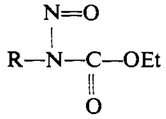
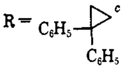
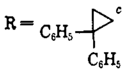
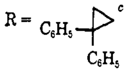
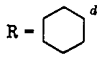
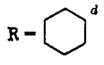
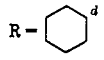
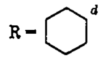
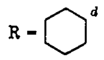
(8) T. K. Tandy, Jr., and W. M. Jones, *J. Org. Chem.*, **30**, 4257 (1965).

(9) A possible reaction scheme other than base attack on the nitroso nitrogen atom that would account for the portion of these reactions that did not go by reaction of ethoxide at the carbonyl carbon involves attack on the carbonyl by hydroxide that is formed as a by-product of the reaction (see Scheme II). However, this possibility was excluded when the reaction was run in the presence of added lithium hydroxide (1 mole) and it was found that the yield of diethyl carbonate was virtually unchanged.

(10) See A. R. Huisgen and H. Reimlinger, *Ann.*, **599**, 183 (1956); A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem Soc.*, **79**, 2893 (1957); and E. H. White and C. A. Aufdermarsh, Jr., *ibid.*, **83**, 1174, 1179 (1961).

Table II.[a] Decomposition of N-Nitroso-N-alkylurethans

Entry	 $R{-}\overset{\overset{N=O}{\vert}}{N}{-}\underset{\underset{O}{\Vert}}{C}{-}OEt$	Solvent	Base	Gas evolution, %	Diethyl carbonate,[b] %
1	 [c]	Et_2O	LiOEt	97	7
2	 [c]	EtOH	LiOEt	52	44
3	 [c]	EtOH	K_2CO_3	31	72
4	 [d]	Et_2O	LiOEt	100	9
5	 [d]	EtOH	LiOEt	100	44
6	 [d]	EtOH	K_2CO_3	98	90
7	 [d]	EtOH	NaOEt	100	70
8	 [d]	EtOH	KOEt	100	78
9	$R = C_6H_5CH_2$[e]	Et_2O	LiOEt	52[f]	10
10	$R = C_6H_5CH_2$[e]	EtOH	LiOEt	46[f]	47
11	$R = C_6H_5CH_2$[e]	EtOH	K_2CO_3	44[f]	52
12	$R = C_6H_5CH_2$[e]	$MeOCH_2CH_2OMe$	LiOEt	42[f]	8
13	$R = C_6H_5CH_2$[e]	$CH_3\underset{\underset{O}{\Vert}}{C}CH_3$	LiOEt	40[f]	14
14	$R = C_6H_5CH_2$[e]	$CH_3\underset{\underset{O}{\downarrow}}{S}CH_3$	LiOEt	46[f]	8
15	$R = C_6H_5CH_2$[e]	$CH_3\underset{\underset{O}{\downarrow}}{S}CH_3$	K_2CO_3	0	No reaction

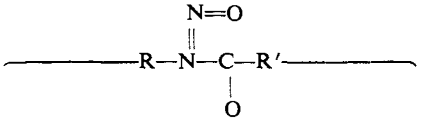
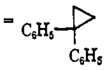
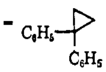
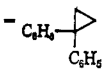
[a] Reactions were run at 25°. Random duplicate runs showed insignificant deviation. [b] Accurate to 3%. [c] Reaction products were 2,2-diphenylcyclopropyldiazotate salts (from attack on the carbonyl carbon) and 1,1-diphenylallene (presumably from collapse of 2,2-diphenyldiazocyclopropane). [d] The formation of diazocyclohexane was shown by running the reaction in diethyl fumarate and isolating the pyrazoline (as its benzoyl derivative). [e] The formation of phenyldiazomethane was shown by allowing it to react with benzaldehyde to give desoxybenzoin. [f] Nitrogen evolution exclusive of phenyldiazomethane decomposition. Upon addition of acetic acid, the phenyldiazomethane was decomposed to lead ultimately to essentially quantitative nitrogen evolution.

the composition of the products resulting from the alkylamine portion of the nitrosobenzylamines is essentially independent of the amount of the reaction that goes by attack of the base on the carbonyl carbon atom as well as the group that is attached to the carbonyl carbon atom. The former of these two results suggests formation of an intermediate from attack on the nitroso nitrogen that is structurally similar to the likely intermediate resulting from attack of the base on the carbonyl carbon—the diazo hydroxide (after protonation). The latter of these two results suggests loss of the group bonded to the carbonyl carbon prior to the product-forming step(s). Both of these conditions are reasonably well met by picturing collapse of the diazo ether instead of the diazo ester.

Supportive evidence for the suggested dual mechanism for the initial phase of the reaction of ethoxide with the nitrosourethans and nitrosoamides resides in the amount of attack of the base on the carbonyl carbon relative to the nitroso nitrogen with variation in the nature of the group attached to the carbonyl carbon atom. Since changes at this point would have a more severe effect on the reactivity of the carbonyl than the nitroso, it would be expected that attack at the carbonyl carbon would decrease (relative to attack at the nitroso) as the attached group is changed from methyl to phenyl (or ethoxy) to NH_2. This prediction is certainly borne out by the experimental results.

Another generality that becomes apparent upon examination of Tables I–III is that in the case of the nitrosourethans and amides, the nature of the solvent has a rather marked effect on the proportion of reaction that proceeds by initial attack of the base on the carbonyl carbon atom. For example, entries 9 and 10 in Table II show that attack by ethoxide on the carbonyl carbon of the benzyl nitrosourethan drops from 47% with lithium ethoxide in ethanol to only 10% with lithium ethoxide in ether. In an attempt to determine if this effect was due to a change in polarity the same reaction was effected in ethylene glycol dimethyl ether, acetone, and dimethyl sulfoxide. In each case, the same results were obtained as found in the reaction in

Table III.[a] Decomposition of N-Nitroso-N-alkylamides

Entry	 $R{-}\overset{N=O}{N}{-}\underset{O}{C}{-}R'$		Solvent	Base	Gas evolution, %	Ethyl carboxylate[b]	Alkali carboxylate[c]
1	R = 	$R' = C_6H_5$[e]	Et_2O	LiOEt	96	4	80
2	R = 	$R' = C_6H_5$[e]	EtOH	LiOEt	58	48	40
3	R = 	$R' = C_6H_5$[e]	EtOH	K_2CO_3	47	56	37
4	$R = C_6H_5CH_2$	$R' = C_6H_5$[f]	Et_2O	LiOEt	48[d]	5	74
5	$R = C_6H_5CH_2$	$R' = C_6H_5$[f]	EtOH	LiOEt	50[d]	44	52
6	$R = C_6H_5CH_2$	$R' = C_6H_5$[f]	EtOH	K_2CO_3	50[d]	54	43
7	$R = C_6H_5CH_2$	$R' = CH_3$	Et_2O	LiOEt	50[d]	7	86
8	$R = C_6H_5CH_2$	$R' = CH_3$	EtOH	LiOEt	46[d]	73	23
9	$R = C_6H_5CH_2$	$R' = CH_3$	EtOH	K_2CO_3	47[d]	83	9

[a] All reactions were run at 25°. Random duplicate runs showed insignificant deviation. [b] Per cent of product resulting from ethoxide attack on the carbonyl carbon atom. [c] Per cent of product resulting from ethoxide attack on the nitroso nitrogen atom. [d] Nitrogen evolution exclusive of phenyldiazomethane decomposition. Upon addition of acetic acid, the phenyldiazomethane was decomposed to lead ultimately to essentially quantitative nitrogen evolution. [e] This compound was synthesized by Dr. T. K. Tandy, Jr. [f] Phenyldiazomethane was shown to be formed by its reaction with benzaldehyde to form desoxybenzoin.

ether (entries 12, 13, and 14 of Table II). Thus, it appears that aprotic solvents favor attack at the nitroso nitrogen whereas protic solvents are more amenable to attack at the carbonyl. Entries 7 and 8 in Table III emphasize this point even more dramatically.

Finally, it should be pointed out (entries 5, 7, and 8 in Table II) that the cation of the base can also have some effect on the relative proportion of carbonyl and nitroso attack. Especially with the cyclohexyl derivative, a change in the cation of the base from lithium to sodium to potassium resulted in an increase in the relative amount of base attack at the carbonyl carbon atom. We offer no explanation for this phenomenon.

In Table IV are summarized the results of a series of experiments that we conducted in an attempt to determine the optimum conditions for the synthesis of diazoalkanes from nitrosoalkylamine derivatives.[11] N-Nitrosobenzylamine derivatives were selected for this study for two reasons. In the first place, under the standard conditions for this type of conversion the reaction of N-nitroso-N-benzylurethan with base is known to undergo an appreciable amount of what is most likely the most serious side reaction in this type of synthesis, ionization of some intermediate to give carbonium ion products.[5] The second reason for studying this particular system is that the diazoalkane is stable whereas the competitive formation of the carbonium ion products involves formation of 1 mole of nitrogen. It was therefore quite convenient to monitor this reaction in a manner similar to that used by Gutsche and Johnson[5] by simply observing nitrogen evolution in an initial phase of the reaction followed by acidification of the product with acetic acid to determine, again by nitrogen evolution, the amount of phenyldiazomethane formed. From this investigation, the following points are worth noting. Although the rate of the reaction is quite sensitive to the nature of the group attached to the carbonyl carbon (the nitrosourea is much more reactive than the urethan or the amide), the yield of phenyldiazomethane is relatively insensitive. However, the yield is influenced by the nature of the solvent (ethanol and ether are superior to hexane), the temperature (lower temperatures favor phenyldiazomethane formation), and the amount of base used (high concentrations of base increase the yield).

Experimental Section

The melting points were taken in a Thomas-Hoover Uni-melt apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer Infracord spectrophotometer and the elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Vapor phase chromatographic analyses were performed with an Aerograph Hy-Fi Model 600-B.

Materials. The solvents (anhydrous ethyl ether, petroleum ether (bp 30–60°), chloroform, acetone, and tetrahydrofuran) used in this work were all Fisher certified reagents and were used without further publication, as were the benzaldehyde and the isoamyl alcohol. The ethyl carbamate (Matheson), the allyl acetate and the cyclohexylurea (K and K), the methanol and the naphthalene (Fisher practical grade), the benzylamine (Eastman practical grade), and the cyclopropanecarboxylic acid and the cyclobutanecarboxylic acid (Aldrich) were also used without further purification, as were the following Eastman White Label chemicals: diethyl fumarate, ethyl chlorformate, cyclohexylamine, desoxybenzoin, and diethyl carbonate. The dimethyl sulfoxide (Matheson) and the ethylene glycol dimethyl ether (Ansul) were freshly distilled before use.

Conditions Used for Vpc Analyses. The two columns used for vpc analyses were: column 1 7% Carbowax 20M on 60–80 mesh Gas Chrom Z (5 ft × 1/8 in.); column 2 20% SE-30 on 60–80 mesh Gas Chrom Z (5 ft × 1/8 in.). The peak areas were determined with a disk chart integrator, and specific conditions required to effect clean separations are listed in Table V.

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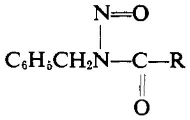
(11) For discussions and lead references on the synthetic aspects of this type of reaction, see: H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Interscience Publishers, Inc., New York, N. Y., 1961, Chapter 1; C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 244; L. I. Smith, *Chem. Rev.*, **23**, 193 (1938); J. Tempe, H. Heslot, and J. Morel, *Compt. Rend.*, **258**, 5470 (1964); R. Huisgen, *Ann.*, **573**, 173 (1951); C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, **28**, 883 (1963); C. D. Gutsche, *Org. Reactions*, **8**, 389 (1954).

Table IV. Conditions for Producing Phenyldiazomethane



$$C_6H_5CH_2N(N{=}O)C(=O)R$$

Entry	R	Solvent	Base	Temp, °C	Gas evolved,[b] %	$C_6H_5CHN_2$,[a] %
1	NH_2	EtOH	LiOEt	−40	29	71
2	NH_2	EtOH	2 moles excess of LiOEt	−20	21	79
3	NH_2	EtOH	LiOEt	−20	35	65
4	NH_2	EtOH	2 moles excess of LiOEt	0	44	56
5	NH_2	EtOH	LiOEt	0	46	54
6	NH_2	EtOH	K_2CO_3	0	49	51
7	NH_2	EtOH	LiOEt	25	48	52
8	NH_2	Et_2O	LiOEt	0	54	46
9	NH_2	Et_2O	2 moles excess of LiOEt	−20	39	61
10	NH_2	Hexane	LiOEt	0	73	27
11	OEt	EtOH	2 moles excess of LiOEt	−20	23	77
12	OEt	EtOH	LiOEt	−20	36	64
13	OEt	EtOH	LiOEt LiOEt	0	45	55
14	OEt	EtOH	K_2CO_3	25	44	56
15	OEt	EtOH	LiOEt	25	46	54
16	OEt	Et_2O	LiOEt	0	46	54
17	OEt	Et_2O	2 moles excess of LiOEt	−20	No reaction	. .
18				0	51	49
19	C_6H_5	EtOH	2 moles excess of LiOEt	−20	23	77
20	C_6H_5	EtOH	LiOEt	−20	36	64
21	C_6H_5	EtOH	LiOEt	0	48	52
22	C_6H_5	EtOH	K_2CO_3	0	48	52
23	C_6H_5	EtOH	LiOEt	25	48	52
24	C_6H_5	Et_2O	LiOEt	0	47	53
25	C_6H_5	Et_2O	2 moles excess of LiOEt	−20	No reaction	. .
26	C_6H_5	Hexane	LiOEt	0	47	53

[a] Yield of phenyldiazomethane corresponds to difference between gas evolved in first step of reaction and theoretical. The validity of this assumption was checked in case of the amides by treating the reaction mixture with acetic acid and measuring the amount of gas evolution. In the case of the ureas, the reaction mixture was treated with benzaldehyde and the amount of gas evolution was measured. In both cases, the total gas evolution was essentially quantitative. Finally, in selected cases (see the Experimental Section) phenyldiazomethane was converted to its *p*-nitrobenzoic acid derivative and isolated. Again, agreement with the values given in the table were satisfactory. [b] Step 1. Nitrogen evolution exclusive of phenyldiazomethane decomposition.

Table V

Compd analyzed	Internal std	Temp, °C	Column
Ethyl carbamate	Menthol	110	1
Diethyl carbonate	Allyl acetate	30	1
Diethyl carbonate	Isoamyl alcohol	30	2
Ethyl benzoate	Naphthalene	115	1
Ethyl acetate	Diethyl carbonate	30	1
Benzyl ethyl ether	Naphthalene	115	1

Urethan Syntheses. Benzylurethan and cyclohexylurethan were prepared by the method of Kurtz and Niemann[12] by treating the appropriate amine with ethyl chloroformate and sodium hydroxide. Benzylurethan had mp 43–44° (lit.[12] mp 44°). Cyclohexylurethan had mp 53–54° (lit.[6] mp 56–56.5°).

2,2-Diphenylcyclopropylurethan was prepared by treating 2,2-diphenylcyclopropyl isocyanate with absolute ethanol in the following way. 2,2-Diphenylcyclopropanecarboxylic acid (16.5 g, 0.070 mole) was converted to the corresponding isocyanate,[13] and 12.9 g (0.28 mole) of absolute ethanol was added to the resulting benzene solution and refluxed for 6 hr. After removing the benzene with a rotary evaporator, the viscous liquid obtained was pumped under a vacuum (1 mm Hg) overnight to effect crystallization. This crude product was obtained as light brown crystals, mp 65–68°, in a yield of 13.5 g (68%). Recrystallization from aqueous methanol gave white needle crystals, mp 74–75°.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 77.02; H, 6.68; N, 5.13.

Benzylurea. Benzylurea was prepared by the method of Boivin and Boivin,[14] using 5.15 g (0.050 mole) of N-nitroso-N-methylurea and 5.35 g (0.050 mole) of benzylamine. The product was obtained as white needle crystals, mp 146–147° (lit.[15] mp 147–147.5°), which separated from the aqueous reaction mixture upon cooling in a yield of 5.05 g (68%).

Cyclobutylurea. Cyclobutylurea was prepared according to the general scheme reported previously[13] from cyclobutanecarbonyl chloride.[16] The intermediate cyclobutanecarbonyl azide and isocyanate were not isolated. The cyclobutylurea was isolated as fine, white needle crystals, mp 166–171°, in a yield of 6.3 g (55% based on starting acid). This crude sample was recrystallized from ethyl acetate to give large, white needle crystals, mp 170–171° (lit.[16] mp 170.5–171°).

Cyclopropylureas. 2,2-Diphenylcyclopropylurea was synthesized by the previously reported method.[13] The unsubstituted cyclopropylurea was synthesized in the same way with the one following exception.

The intermediate cyclopropanecarboxylic acid chloride was fractionally distilled from unreacted thionyl chloride. The acid chloride was collected at 47° (55 mm) (the thionyl chloride distilled at 33–35° (65–75 mm)). The desired urea was obtained as needle crystals melting at 124° (24%) (lit.[17] mp 123–124°).

Amide Syntheses. N-Benzylacetamide (mp 60–61°) and N-benzylbenzamide (mp 104–105°) were prepared by routine acylation means. N-(2,2-Diphenylcyclopropyl)benzamide was prepared in the following way. A benzene solution of 2,2-diphenylcyclopropyl isocyanate, made in the usual manner from 2,2-diphenylcyclopropanecarboxylic acid (10.0 g, 0.042 mole), was cooled to 0° and maintained in an atmosphere of dry argon as a slight excess of phenylmagnesium bromide in ether was slowly added with stirring. After stirring for 1 hr, the reaction mixture was allowed to warm to room temperature and stir for 1 additional hr. The solution was then cooled to 0° and an aqueous solution of 2.61 g (0.0488 mole) of ammonium chloride was added. The organic layer was separated, washed successively with 5% HCl, 5% $NaHCO_3$, and water, dried over anhydrous magnesium sulfate, and evaporated to a solid residue. The solid was leached with pentane and filtered to give 9.53 g (72.5% from acid) of product amide, mp 156–158°. Successive recrystallizations from hot benzene or benzene-pentane gave analytically pure product, mp 157–158°.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.27; H, 6.08; N, 4.31.

Preparation of N-Nitroso-N-alkylureas. The following general procedure for nitrosation of alkylureas is a modification of White's[18] method. In a typical preparation, 1.00 g (0.010 mole) of cyclopropylurea and 0.82 g (0.010 mole) of anhydrous sodium acetate were stirred in 15 ml of anhydrous ether at −50°. A solution of dinitrogen tetroxide (0.92 g, 0.010 mole) in ether (prepared by passing the gas into a tared volumetric flask about one-half full with ether at −50° and noting the increase in weight) was then added with a syringe through a rubber septum. The blue color of the oxide slowly faded during 30 min of stirring, leaving a green solution which changed to yellow as the temperature was allowed to rise to −20°. After filtering off the inorganic residue, the filtrate was then washed with 5% aqueous sodium bicarbonate to remove

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[12] A. N. Kurtz and C. N. Niemann, *J. Org. Chem.*, **26**, 1834 (1961).

[13] W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *J. Am. Chem. Soc.*, **85**, 2754 (1963).

[14] J. L. Boivin and P. A. Boivin, *Can. J. Chem.*, **29**, 478 (1951).

[15] I. Heilbron, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, N. Y., 1953.

[16] D. E. Appelquist and D. E. McGreer, *J. Am. Chem. Soc.*, **82**, 1965 (1960).

[17] V. P. Gol'mov, *J. Gen Chem. USSR*, **5**, 1562 (1935).

[18] E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

the acetic acid, then with water, and finally dried over anhydrous magnesium sulfate. Filtration with suction followed by removal of the ether from the filtrate on a rotary evaporator gave the product as a solid, mp 95–98° dec. By not removing quite all of the ether, the nitrosourea could be precipitated by the addition of pentane. This procedure gave yellow crystals, mp 104° dec, in a yield of 0.95 g (74%). Recrystallization from a chloroform–pentane solvent mixture gave fine, yellow needle crystals, mp 108° dec.

Anal. Calcd for $C_4H_7N_3O_2$: C, 37.21; H, 5.43; N, 32.56. Found: C, 36.87; H, 5.67; N, 32.87.

This compound had been reported earlier to have a melting point of 86° dec.[17] All of the nitrosoureas used have been previously reported although some of the reported nitrosations were carried in a different way from that given above. The alkyl group, melting point, reported melting point, and yield by the above method are: cyclobutyl, mp 66–67° (lit.[16] mp 67–69°), yield 39%; 2,2-diphenylcyclopropyl, mp 114–115° (lit.[13] mp 114–115°), 78% yield; cyclohexyl, mp 116° (lit.[19] mp 116°), 24% yield; benzyl, mp 100–101° (lit.[20] mp 101°), 66% yield.

Preparation of N-Nitroso-N-alkylurethans. The nitrosourethans were all prepared by the method of White[18] using dinitrogen tetroxide in ether at −30°. In a typical preparation, 3.58 g (0.0020 mole) of benzylurethan was dissolved in 20 ml of anhydrous ether which was stirred at −30° over 1.64 g (0.0020 mole) of anhydrous sodium acetate. To this solution was added a solution of 1.84 g (0.0020 mole) of dinitrogen tetroxide in ether (prepared by blowing the gaseous oxide into a tared volumetric flask containing a little ether at −50° and recording the increase in weight). Stirring was continued at −30° for 30 min or until the solution turned from blue to yellow. Warming to 0° over 10 min completed any slow reactions. After filtering off the inorganic salts, this solution was then washed with 5% aqueous sodium bicarbonate, then with water, and finally dried over sodium sulfate. Removal of the solvent on a rotary evaporator gave 3.90 g (94%) of a yellow oil which showed no N–H infrared absorption at 2.85 μ, n^{23}D 1.5155 (lit.[12] n^{25}D 1.5166).

All of the nitrosourethans were yellow oils. Absence of unnitrosated urethan was demonstrated by tlc and infrared analyses. The index of refraction of the cyclohexyl derivative compared satisfactorily with the reported[6] value.

Preparation of N-Nitroso-N-alkylamides. The general procedure of White[18] was used in the preparation of the nitrosamides from the corresponding alkylamides. In a typical preparation, N-benzylbenzamide (2.11 g, 0.010 mole) was dissolved in glacial acetic acid and cooled to 0–5°. To this was added 1.64 g (0.020 mole) of anhydrous sodium acetate and 0.92 g (0.010 mole) of dinitrogen tetroxide in ether. When the green color of the reaction mixture had disappeared, water was added, the mixture was extracted with ether, and the ether was washed thoroughly with water, sodium bicarbonate, and water, and then dried over magnesium sulfate. Removal of the ether normally gave yellow oils which were analyzed for unreacted amide by tlc and infrared. The tlc plate invariably showed only one spot and the infrared showed no absorption in the 3.0-μ region. N-Nitroso-N-benzylbenzamide was isolated as a yellow solid, mp 45–47° (lit.[21] mp 46–47°). N-Nitroso-N-benzylacetamide has also been reported in the literature[22] as a yellow oil.

Base-Induced Decomposition of N-Nitroso-N-alkylureas. In a typical experiment, 0.171 g (0.0010 mole) of N-nitroso-N-cyclohexylurea was dissolved in 15 ml of ether and cooled to 0°. To this was added *via* a solid addition attachment 0.052 g (0.0010 mole) of lithium ethoxide in one portion. Gas evolution was measured and stirring was continued until gas evolution had ceased. Filtration of the reaction mixture gave 88% of a white solid whose infrared spectrum was identical with lithium cyanate. Vpc analysis of the filtrate using menthol as an internal standard showed no ethyl carbamate. Under these conditions, 2% would have been easily detected.

The other reactions with base were carried out in essentially the same manner with the following exceptions. In the decomposition of N-nitroso-N-cyclobutylurea, the lithium ethoxide was dissolved in 2 ml of absolute ethanol before its addition. This was in order to duplicate the experimental conditions reported by Applequist and McGreer.[16] In the decomposition of N-nitroso-N-benzylurea, after the gas evolution had ceased, benzaldehyde was added through a septum until the remainder of the gas evolution was complete. This was necessary in this case because phenyldiazomethane is stable to the conditions of the reaction.

Base-Induced Decompositions of N-Nitroso-N-alkylurethans. These reactions were run in essentially the same way as the decompositions of the ureas with the single exception that isoamyl alcohol was used as the internal standard for the diethyl carbonate analyses.

In one case, N-nitroso-N-benzylurethan (0.416 g, 0.0020 mole) was dissolved in absolute ethanol and added to a solution of 0.104 g (0.0020 mole) of lithium ethoxide and 0.048 g (0.0020 mole) of lithium hydroxide in 20 ml of absolute ethanol. Formation of a deep red color and the evolution of 23 ml (48%) of nitrogen was complete in 5 min. The phenyldiazomethane was decomposed with acetic acid and the resulting mixture was analyzed for diethyl carbonate (55%) in the usual manner.

The Base-Induced Decomposition of N-Nitroso-N-(2,2-diphenylcyclopropyl)benzamide. In each run shown in the first three entries in Table III, 0.316 g (0.0010 mole) of N-nitroso-N-(2,2-diphenylcyclopropyl)benzamide was stirred in 15 ml of the solvent at room temperature. The base, either lithium ethoxide (0.052 g, 0.0010 mole) or potassium carbonate (0.138 g, 0.0010 mole), was then quickly added and the closed system was monitored for gas evolution. After gas evolution had ceased, the reaction mixture was filtered if necessary, and the resulting solution was then analyzed for ethyl benzoate on the vpc (using naphthalene as the internal standard). The stability of ethyl benzoate to the reaction conditions was confirmed by treating 0.0020 mole of ethyl benzoate with 0.0020 mole of lithium hydroxide in ethanol at room temperature for 8 hr. Ethyl benzoate (84%) was recovered. When ether was the solvent, the benzoate salts precipitated from the reaction solution. For the runs made in alcohol, the solvent had to be evaporated on a rotary evaporator in order to check for additional products. The residue obtained by this procedure was triturated with ether and filtered to give the alkali benzoates. The yield of benzoates was determined by dissolving the salts in water, acidifying with 1 *N* hydrochloric acid, and extracting the benzoic acid with ether. The yields are given in Table III.

The ether filtrate obtained by trituration of the crude reaction product was evaporated to a gummy oil, and this material was then triturated with pentane to give the 2,2-diphenylcyclopropyldiazotate salt as a white solid. After filtering the diazotate, the pentane filtrate was evaporated to give 1,1-diphenylallene as a light yellow oil. Both the allene and the diazotate were identified by comparison of their infrared spectra with those of the known materials.[3,13]

The Base-Induced Decomposition of N-Nitroso-N-benzylbenzamide. In each run listed in Table III (entries 4–6), 0.480 g (0.0020 mole) of N-nitroso-N-benzylbenzamide was stirred in 15 ml of the solvent at room temperature. The base, either lithium ethoxide (0.104 g, 0.0020 mole) or potassium carbonate (0.276 g, 0.0020 mole), was then quickly added and the closed system was monitored for gas evolution. After gas evolution had ceased, the reaction mixture was filtered if necessary and benzaldehyde or acetic acid was added to decompose the phenyldiazomethane. The resulting solution was then analyzed for ethyl benzoate with the vpc, using naphthalene as the internal standard. Since benzyl ethyl ether was a product of the runs made in ethyl alcohol, its yield was also determined on the vpc using the naphthalene as the internal standard. The yields compared satisfactorily with the gas evolution. For the runs made in alcohol, the solvent had to be evaporated on a rotary evaporator in order to check the salts present. The yields of alkali benzoates were determined by dissolving the salts in water, acidifying with 1 *N* hydrochloric acid, and extracting the benzoic acid with ether. Vpc conditions allow an accuracy of ±3% on both analyses.

The Base-Induced Decomposition of N-Nitroso-N-benzylacetamide. For each decomposition shown in Table III (entries 7–9), 0.356 g (0.0020 mole) of N-nitroso-N-benzylacetamide was stirred in 15 ml of the solvent at room temperature. The base, either lithium ethoxide (0.104 g, 0.0020 mole) or potassium carbonate (0.276 g, 0.0020 mole), was then quickly added and the closed system was monitored for gas evolution. After gas evolution had ceased, the reaction mixture was filtered if necessary and benzaldehyde was added to decompose the phenyldiazomethane. The resulting solution was then analyzed for ethyl acetate by vpc, using diethyl carbonate as the internal standard. Since benzyl ethyl ether was a product of the runs made in ethyl alcohol, its yield was also determined on the vpc using the diethyl carbonate already present as the internal standard. For the runs made in alcohol, the solvent

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[20] E. A. Werner, *J. Chem. Soc.*, **115**, 1093 (1919).
[21] C. Blacher, *Ber.*, **28**, 434 (1895).
[22] H. Amsel and A. W. Hofmann, *ibid.*, **19**, 1286 (1886).

had to be evaporated on a rotary evaporator in order to check the salts present. The alkali acetates were identified by comparison of their infrared spectra with those of the known salts. Conditions of the vpc analyses allow ±5% accuracy.

Preparation of Phenyldiazomethane and Isolation as Its *p*-Nitrobenzoyl Derivative. N-Nitroso-N-benzylurea (1.79 g, 0.010 mole) was dissolved in 25 ml of absolute ethanol. The mixture was cooled to −20° and 1.56 g (0.030 mole) of lithium ethoxide was added. The mixture was stirred at −20° until gas evolution ceased (53 ml, 22%). *p*-Nitrobenzoic acid was then added to the red solution until the color disappeared. The ethanol was then removed with a rotary evaporator and the residue was taken up in ether–water. The ether layer was washed with 5% sodium bicarbonate solution followed by water and dried over magnesium sulfate. Removal of the solvent gave 1.88 g (73%) of a residue (mp 78–81°) whose infrared spectrum was essentially identical with that of pure benzyl *p*-nitrobenzoate, mp 82–83° (from ethanol) (lit.[23] mp 82–82.5°).

The above reaction was repeated in ether under identical conditions to give 40% gas evolution in the first step and 58% of isolated ester.

Reaction of Phenyldiazomethane with Benzaldehyde. A solution of phenyldiazomethane was prepared by decomposing 1.79 g (0.010 mole) of N-nitroso-N-benzylurea dissolved in 50 ml of absolute ethanol at −20° with 0.52 g (0.010 mole) of lithium ethoxide. Gas evolution ceased in 5–10 min after 81 ml (34%) had been collected. The solution was then warmed to room temperature and 1.06 g (0.010 mole) of benzaldehyde (freshly distilled) was added with stirring. Stirring was continued for 1 hr, during which time 156 ml of gas were evolved (65%). After removing the ethanol with a rotary evaporator, the residual oil was taken up in ether and washed twice with 10 ml of 40% aqueous sodium bisulfite solution, once with water, and dried over anhydrous magnesium sulfate. Removal of the ether on a rotary evaporator gave a crude white solid, mp 53–55°, in a yield of 0.94 g (74%, based on the assumption that 0.0065 mole of diazoalkane was present). Recrystallization from methanol gave white plates, mp 55–56° (lit.[24] mp 55–56°). The infrared spectrum of this material was identical with that of a known sample of desoxybenzoin.

A similar procedure was used to prepare phenyldiazomethane from N-nitroso-N-benzylurethan and N-nitroso-N-benzylbenzamide, and the same results were obtained with only small variations in yields.

1-Benzoyl-3,4-dicarbethoxy-5,5-dimethylene-2-pyrazoline. N-Nitroso-N-cyclopropylurea (0.516 g, 0.00400 mole) was dissolved in 15 ml of diethyl fumarate and stirred at 50–60° overnight while collecting evolved gases in a graduated tube. A colorless solution resulted with negligible gas evolution. This solution was passed through a column of Woelm acid-washed alumina (15 mm × 18 cm) using pentane as the eluent. When all of the unreacted diethyl fumarate had been removed, the eluent was changed to ether containing 2% methanol. About 100 ml of solvent removed the pyrazoline from the column. The solvent was then removed on a rotary evaporator to give an oil which readily turned yellow on exposure to air. This oil was dissolved in 5 ml of anhydrous pyridine and 1 ml of benzoyl chloride was added followed by refluxing overnight. The resulting dark solution was poured into water and stirred for 3 hr to remove the unreacted acid chloride. Extraction with ether followed by washing the extracts with 5% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate, and then with water gave a deep red oil when the dried solvent was evaporated. This oil was chromatographed over Woelm acid-washed alumina using ether as the eluent. Eight samples were collected with thin layer chromatography showing the second to be essentially pure. Scratching of this oil under 95% ethanol at Dry Ice temperature gave a white precipitate. Suction filtration gave a white solid, mp 90–92°, which was recrystallized from ethanol to give 0.0500 g of white needles, mp 92–93°. This material exhibited ultraviolet absorption maxima in methanol at 237 mμ (ε 6830) and 302 mμ (ε 14,200). Significant infrared absorptions are (KBr): 5.73, 5.84, 6.03, and 6.34 μ.

Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.57; H, 5.69; N, 8.14.

1-Benzoyl-3,4-dicarboethoxy-5,5-pentamethylene-2-pyrazoline. N-Nitroso-N-cyclohexylurethan (4.00 g, 0.020 mole) was diluted with 10 ml of diethyl fumarate and, while stirring at room temperature, 1.04 g (0.020 mole) of lithium ethoxide was added in a few portions. This solution was then stirred overnight at room temperature. After diluting the resulting solution with ethyl ether, it was washed twice with 5% aqueous sodium bicarbonate and once with water, and dried over anhydrous magnesium sulfate. When the ether had been removed on a rotary evaporator the fumarate solution was chromatographed over alumina (Woelm, acid washed; column 20 mm × 40 cm) using hexane as eluent for the fumarate which came through rapidly. Elution with ether containing 1% methanol gave 150 ml of solution which was reduced to a yellow oil with a rotary evaporator. An infrared spectrum of this oil showed significant absorptions at 2.95, 5.8 (broad), and 6.45 μ, indicating that the 2-pyrazoline had been formed. Attempts to crystallize this oil were unsuccessful, so the benzoyl derivative was prepared by dissolving the oil in refluxing anhydrous pyridine containing 2 ml of benzoyl chloride. After refluxing overnight, the resulting solution was stirred in 50% ethanol–water to hydrolyze the benzoyl chloride, and the ethanol was removed with a rotary evaporator. This aqueous mixture was extracted with ether, and the extracts washed twice with 1 *N* hydrochloric acid, twice with 5% aqueous sodium bicarbonate, and once with water before drying over anhydrous magnesium sulfate. Evaporation of the solvent on a rotary evaporator left a small amount of light yellow oil which was chromatographed through alumina (Woelm, acid washed; column 15 mm × 30 cm) using hexane as eluent for the remaining diethyl fumarate followed by ether. The first cuts to come through after the fumarate showed one spot only on thin layer chromatography (silica gel, ether as developing solvent). When these cuts were combined and the solvent was evaporated, a clear oil remained which crystallized from ethanol–water, mp 85–88°. Recrystallization from ethanol–water gave 0.023 g of white needle crystals, mp 88–89°. This material exhibited ultraviolet absorption maxima at 224 mμ (ε 14,300) and 287 mμ (ε 22,300) in methanol. Significant infrared absorptions are (KBr): 5.78, 5.84, 6.01, and 6.28 μ.

Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.29; H, 6.74; N, 7.25. Found: C, 65.07; H, 6.64; N, 7.06.

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[24] B. Allen, *Org. Syn.*, **12**, 16 (1932).