[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Ring Enlargements. III. Ring Enlargement of Cyclohexanone with Ethyl N-Nitroso-N-Benzylcarbamates Carrying Methyl and Methoxyl Substituents on the Phenyl Nucleus

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A study has been made of the ring enlargement of cyclohexanone in methanol with several ethyl N-nitroso-N-benzylcarbamates carrying methyl and methoxyl substituents on the phenyl nucleus. The ratio of $ArCH_2OCH_3$ to 2-arylcycloheptanone formed increases in the following order of Ar: phenyl $\simeq$ *m*-methoxyphenyl < *o*-methylphenyl < *p*-methylphenyl < *o*-methoxyphenyl < *p*-methoxyphenyl < 2,3,4-trimethoxyphenyl $\simeq$ 2,4,6-trimethylphenyl. A mechanism is proposed which accommodates the substituent effect as well as other features of the reaction.

The failure of ethyl N-nitroso-N-(2,3,4-trimethoxybenzyl)-carbamate (IE) to react with cyclohexanone to yield 2-(2',3',4'-trimethoxyphenyl)-cycloheptanone[2] prompted further study of this type of reaction, and in this communication the results with several additional ethyl N-nitroso-N-benzylcarbamates are described.

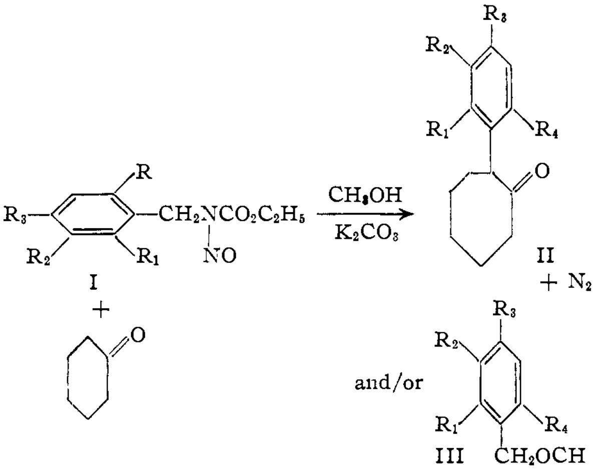


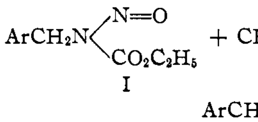
TABLE I

PRODUCTS FROM ETHYL N-NITROSO-N-BENZYLCARBAMATES METHANOL AND CYCLOHEXANONE

Starting compound (I)	R_1	R_2	R_3	R_4	N_2 evolved in 2nd phase	2-Arylcycloheptanone (II)	Methyl arylmethyl ether (III)
A	H	H	H	H	38	41	27
B	CH_3O	H	H	H	41	41	32
C	H	CH_3O	H	H	28	29	37
D	H	H	CH_3O	H	21	26	45
E	CH_3O	CH_3O	CH_3O	H	16	20	50
F	CH_3	H	H	H	9	7	64
G	H	H	CH_3	H	1-10	0	72
H	CH_3	H	CH_3	CH_3	0	0	62

The benzylamines required for this study were prepared readily by standard methods and were converted easily to the ethyl N-nitrosocarbamates by treatment with ethyl chlorocarbonate followed by nitrosation with nitrous acid. Reactions with cyclohexanone in the presence of methanol and potassium carbonate were then carried out, and the products were fractionated carefully to determine the amounts of 2-arylcycloheptanone (II) and methyl arylmethyl ether (III) formed. The results of these experiments are summarized in Table I.

Discussion of Results.—One of the standard methods for effecting ring enlargements employs a nitrosocarbamate, a base and a cycloalkanone[3]; the probable reaction sequence involves the base-catalyzed conversion of the nitrosocarbamate to a diazoalkane which then interacts with the ketone. That the diazoalkane is the common intermediate in the formation of II and III, however, is excluded by the observation that pure phenyldiazomethane reacts only to a negligible extent with methanol (with or without added potassium carbonate) but reacts rapidly with cyclohexanone in methanol to form IIA in high yield.[4] The common intermediate must instead occur at some prior step in the conversion of I to the diazoalkane, and the following scheme is suggested[5]



$$(1)\quad ArCH_2N\begin{matrix}N{=}O\\ CO_2C_2H_5\end{matrix}\underset{I}{} + CH_3O^{\ominus} \longrightarrow \underset{IV}{ArCH_2N{=}NO^{\ominus}} + CH_3OCO_2C_2H_5$$

$$(2)\quad \underset{IV}{ArCH_2N{=}NO^{\ominus}} + CH_3OH \rightleftarrows \underset{V}{ArCH_2N{=}NOH} + CH_3O^{\ominus}$$

$$(3a)\quad \underset{V}{ArCH_2N{=}NOH} + CH_3O^{\ominus} \rightleftarrows Ar\overset{\ominus}{C}HN{=}NOH + CH_3OH$$

$$\downarrow$$

$$ArCHN_2 + OH^{\ominus}$$

$$ArCHN_2 + C_6H_{10}O \longrightarrow II + N_2$$

$$(3b)\quad \underset{V}{ArCH_2N{=}NOH} \rightleftarrows ArCH_2^{\oplus} + [N_2OH]^{\ominus} \longrightarrow N_2 + OH^{\ominus}$$

$$ArCH_2^{\oplus} + CH_3OH \longrightarrow ArCH_2OCH_3 + H^{\oplus}$$

(1) The base-catalyzed decomposition of nitrosocarbamates is a well-known reaction, and in a few instances the potassium diazotates have even been isolated. Ethyl N-nitroso-N-benzylcarbamate (IA),

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[1] Petrolite Corporation Fellow, 1952–1953.

[2] C. D. Gutsche and H. E. Johnson, THIS JOURNAL, **76**, 1776 (1954).

[3] C. D. Gutsche, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y.

[4] C. D. Gutsche and E. F. Jason, forthcoming publication.

[5] It is interesting to compare certain aspects of this scheme with one recently proposed by M. S. Newman and W. M. Edwards, THIS JOURNAL, **76**, 1840 (1954), for the base-catalyzed decomposition of 3-nitroso-2-oxazolidones.

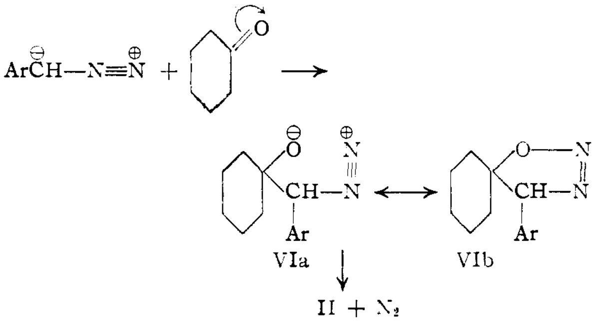
for instance, is converted to the isolable potassium salt of IV upon treatment with concentrated potassium hydroxide at low temperature.[6] The base in the present system is presumed to be the methoxide anion formed from the solution of potassium carbonate in and reaction with methanol according to the scheme: $K_2CO_3 + CH_3OH \rightleftarrows KHCO_3 + CH_3OK$.

(2) The potassium salt of IV shows a strong tendency to undergo solvolysis, and treatment with water or ethanol induces the formation of phenyldiazomethane and benzyl alcohol or ethyl benzyl ether.[6] The present proposal assumes the diazo hydroxide V to be the initial product from the solvolysis and that V then reacts in one or both of two ways to form II and/or III.

(3a) One possible mode of reaction of V involves the loss of water to yield the diazoalkane which then reacts with cyclohexanone to form II. Little is known concerning the mechanism of dehydration of such systems, but it may follow the E2 course with attack of a base on a hydrogen attached to the benzyl carbon atom followed by expulsion of the hydroxyl group from the nitrogen. If so, it would constitute an interesting example of the E2 reaction in which a five-center instead of the usual four-center or the less usual six- or eight-center system is involved.[7] It is well known that reactions of this general type are aided by electron-withdrawing substituents and hindered by electron-donating substituents.[8] Thus, *o*-methyl, *p*-methyl and *p*-methoxyl groups should retard the dehydration while a *m*-methoxyl group might aid it. The *o*-methoxyl group is more difficult to assess; it imposes a strong inductive electron withdrawal in opposition to its resonance-electromeric electron donation and would be expected to impede the dehydration to a lesser extent than the *p*-methoxyl group. This may, in part, explain the greater amount of II formed from IB than from ID.

(3b) A second possible mode of reaction of V involves a monomolecular (or pseudo-monomolecular) decomposition to a benzyl carbonium ion and a N_2OH^- anion followed by reaction of the former with methanol to yield the ether III. Driving force for the ionization should derive from the instability of the anion (decomposing to nitrogen and hydroxyl ion) and from anything that enhances the stability of the benzylcarbonium ion. Substituents such as the *p*-methyl and *p*-methoxyl groups are well known for their ability to promote reactions involving ionizations of this type.[8a,9] Thus, as the electron-donating power of the substituent groups increases, the preference of reaction path 3b over 3a becomes greater. The relatively weakly electron-donating methyl groups in the *o*- and *p*-positions only slightly reduce the yield of II and increase the yield of III. The more strongly electron-donating methoxyl groups in the *o*- and *p*-positions have a greater effect, particularly in the case of the *p*-methoxy compound. Conversely, a methoxyl group in the *m*-position can exert an effect on the benzyl position only through the rather weak inductive route (and as such, would be electron-withdrawing) and consequently has little effect on the outcome of the reaction. A multiplicity of methyl or methoxyl groups enhances the effect to the point where *only route 3b is followed.* In the case of the 2,4,6-trimethyl derivative steric effects are probably also important, however, and the stabilization of the carbonium ion may be due to a combination of the inductive effect, hyperconjugative resonance contribution, and B-strain as has been suggested for various alkyl carbonium ions.[10]

The nitrogen evolution during the reaction of I with cyclohexanone occurs in two phases, a rapid first phase during the period in which I is being added to the reaction mixture (15 minutes) followed by a slow second phase (several hours). The amount of nitrogen given off in the second phase closely parallels the amount of 2-arylcycloheptanone (II) formed and is thought to be the result of either the slow addition of the diazoalkane to the cyclohexanone or the slow decomposition of an intermediate VI indicated in the scheme



Some evidence for the existence of a labile, nitrogen-containing intermediate VI is available as, for instance, the observation that chloral reacts with ethereal diazomethane to form an addition product (in solution) which is not decomposed by benzoic acid but which loses nitrogen upon heating or evaporation of the ether.[11]

The proposed mechanism for the reactions thus accommodates the following observations: (a) Ethyl N-nitroso-N-benzylcarbamate is unreactive in methanol alone but decomposes upon the addition of potassium carbonate. (b) Ethyl N-nitroso-N-benzylcarbamate reacts with cyclohexanone in methanol containing potassium carbonate to give a mixture of ketone II and ether III. (c) Phenyldiazomethane is unreactive toward methanol with or without added potassium carbonate but reacts with a methanolic solution of cyclohexanone to give

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(6) A. Hantzsch and M. Lehmann, *Ber.*, **35**, 897 (1902).

(7) A related four-center elimination reaction is the dehydrobromination of 2-phenylethyl bromide which has been shown to involve the bimolecular E2 mechanism—E. D. Hughes, C. K. Ingold, S. Masterman and B. J. MacNulty, *J. Chem. Soc.*, 899 (1940). Six- and eight-center elimination reactions are known and recently have been studied—W. M. Schubert, T. H. Liddicoet and W. A. Lanka, *Science*, **116**, 124 (1952); THIS JOURNAL, **76**, 1929 (1954).

(8) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184 ff.; (b) C. R. Hauser, J. W. LeMaistre and A. E. Rainsford, THIS JOURNAL, **57**, 1056 (1935).

(9) (a) S. C. J. Olivier, *Rec. trav. chim.*, **41**, 301 (1922); (b) J. F. Norris and C. Banta, THIS JOURNAL, **50**, 1804 (1928).

(10) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 41.

(11) F. Schlotterbeck, *Ber.*, **42**, 2559 (1909); F. Arndt, B. Eistert and W. Ender, *ibid.*, **62**, 44 (1929); H. Meerwein, T. Bersin and W. Burneleit, *ibid.*, **62**, 999 (1929).

high yields of II.[12] (d) When I reacts with cyclohexanone, nitrogen is evolved in two phases, and the second phase evolution agrees closely with the amount of II formed. (e) Electron-donating groups on the phenyl nucleus and/or bulky *ortho* substituents increase the amount of III and decrease the amount of II formed from I. The excellence of methanol as a reaction medium may be due to its ability to coördinate with the ketone and thereby facilitate the nucleophilic attack of the diazoalkane.[13] Further work is necessary, however, to ascertain the full role of the solvent in reactions of this type.

Experimental[14–16]

Preparation of the Ethyl N-Nitroso-N-benzylcarbamates (I). Ethyl N-(2-Methoxybenzyl)-carbamate.—2-Bromoanisole was converted in 71% yield to 2-methoxybenzonitrile by the method described in the previous paper.[2]

Lithium aluminum hydride reduction produced 2-methoxybenzylamine in 47% yield, and this was treated with ethyl chlorocarbonate according to the procedure of Hartman and Brethen[17] to produce the carbamate in 96% yield crude, 83% yield after distillation; b.p. 117–118° (0.5 mm.), n^{25}D 1.5218.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 62.81; H, 7.20.

Nitrosation by the general procedure of Hartman and Phillips[18] but with extension of the time to 6 hours and increase of the temperature to 15–20° gave IB as a red-orange oil in 95% yield.

Ethyl N-(3-Methoxybenzyl)-carbamate.—A lithium aluminum hydride reduction of *m*-methoxybenzamide (m.p. 130–131.5°) gave a 57% yield of *m*-methoxybenzylamine, b.p. 117–120° (12 mm.), n^{25}D 1.5450. A picrate with m.p. 185–186° was obtained (reported[19] 181°). The amine was converted to the carbamate (94.5% yield), which was obtained as a colorless liquid, b.p. 123–125° 0.2 mm., n^{25}D 1.5208.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.31; H, 7.00.

Nitrosation gave IC as an orange-red oil in nearly quantitative yield.

Ethyl N-(4-methoxybenzyl)-carbamate was obtained in 87.5% yield from 4-methoxybenzylamine; b.p. 117–119° (0.20 mm.), m.p. 37–39°. Two recrystallizations from ether-petroleum ether (b.p. 32–37°) gave glistening, white plates, m.p. 40–41°.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.18; H, 7.15.

Nitrosation yielded 99% of ID as a mobile, red-orange oil.

Ethyl N-(2-methylbenzyl)-carbamate was obtained in 92% yield from 2-methylbenzylamine; b.p. 100–101° (0.3 mm.), n^{25}D 1.5182. A portion was recrystallized twice from petroleum ether (b.p. 63–69°) and was obtained as glistening, white plates, m.p. 33–34°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.43; H, 7.77.

Nitrosation proceeded in 98% yield to give IF as a mobile, red-orange oil.

Ethyl N-(4-methylbenzyl)-carbamate was obtained in 96% yield from 4-methylbenzylamine; m.p. 55–57°. Two recrystallizations from petroleum ether (b,p. 63–69°) gave stout, white needles, m.p. 57.5–58.5°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.60; H, 7.90.

Nitrosation gave 100% of IG as a mobile, orange oil.

Ethyl N-(2,4,6-trimethylbenzyl)-carbamate was obtained in 91% yield from 2,4,6-trimethylbenzylamine; m.p. 106–109°. Several recrystallizations from aqueous ethanol gave stout needles, m.p. 110–111°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.37; H, 8.79.

The nitrosation was carried out by the usual procedure except that an 8-hour reaction period was employed and the temperature was maintained at 20–25°. The product, obtained in 96% yield, was a yellow solid, m.p. 76–79°. Three recrystallizations from cold methanol gave feathery, pale yellow needles of IH, m.p. 83–84°.

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 62.38; H, 7.25. Found: C, 62.41; H, 7.31.

Reactions of I with Cyclohexanone and Methanol.—The following procedure was used in all cases. In a 300-ml., 3-necked round-bottomed flask fitted with a sealed stirrer, an addition funnel and a condenser leading to a eudiometer tube was placed 16 g. (0.16 mole) of cyclohexanone, 40 ml. of absolute methanol and 1 g. of finely powdered, anhydrous potassium carbonate. To the stirred mixture there was added, over a period of 15 minutes, 0.075 mole of the ethyl N-nitroso-N-benzylcarbamate (I) during which time the temperature was maintained at 25° by means of a cold water-bath. The reaction mixture was then allowed to stand at 25° until the evolution of nitrogen ceased (0–48 hours depending upon the particular reaction). The potassium carbonate was removed by filtration, the solvents were removed under reduced pressure and the residue was distilled through a 12-inch, glass helix-packed column to separate the cyclohexanone from the ether III. The higher-boiling fraction, containing the 2-arylcycloheptanone II, was distilled through a Claisen head. The amount of II and III obtained totalled to 62–73% with the remaining material accounted for as intermediate fractions (*ca.* 20%) and still pot residue (*ca.* 10%). All of the experiments were carried out at least in duplicate.

Ethyl N-nitroso-N-benzylcarbamate (IA) reacting with cyclohexanone has been reported previously,[20] but the experiment was repeated in order to ascertain the amount of IIIA formed. From the crude product there was obtained 41% of 2-phenylcycloheptanone (IIA) and a fraction with b.p. 63–75° (30 mm,) containing a mixture of cyclohexanone (n^{25}D 1.4480) and benzyl methyl ether (n^{25}D 1.5021). The mixture had n^{25}D 1.4634 from which it can be calculated that 29% of IIIA was formed.

Ethyl N-nitroso-N-(2-methoxybenzyl)-carbamate (IB) yielded (a) 50% of **2-methoxybenzyl methyl ether (IIIB)**, b.p. 53–54° (0.25 mm.), n^{25}D 1.5151. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95; CH_8O, 40.8. Found: C, 70.55; H, 7.76; CH_3O, 41.2.

(b) 20% of 2-(2′-methoxyphenyl)-cycloheptanone (IIB); b.p. 115–117° (0.20 mm.), n^{25}D 1.5381. Redistillation gave material with b.p. 116° (0.40 mm.), n^{25}D 1.5407. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.29.

The 2,4-dinitrophenylhydrazone of IIB was obtained as yellow crystals after several recrystallizations from ethanol, m.p. 178–179°.

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 60.29; H, 5.57. Found: C, 60.39; H, 5.58.

Ethyl N-nitroso-N-(3-methoxybenzyl)-carbamate (IC) yielded (a) 32% of **3-methoxybenzyl methyl ether (IIIC)**, b.p. 52–53° (0.3 mm.), n^{25}D 1.5115. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.14; H, 7.98.

(b) 41.5% of **2-(3′-methoxyphenyl)-cycloheptanone (IIC)**, b.p. 119–121° (0.3 mm.), n^{25}D 1.5418. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.27.

The 2,4-dinitrophenylhydrazone of IIC was obtained as

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(12) On the basis of the colors observed during the reactions discussed in a previous paper (*cf.* ref. 2) it was stated that IIIE must arise from the diazoalkane as the intermediate. The present work shows this to be incorrect, and suggests that the colors may arise from some of the other reaction intermediates such as $ArCH_2^+$.

(13) H. Meerwein and W. Burneleit, *Ber.*, **61**, 1840 (1928).

(14) All melting points are corrected.

(15) The microanalyses were performed by Mr. William Parr of this Laboratory, by the Micro-Tech Laboratories of Skokie, Ill., and by Weiler and Strauss of Oxford, England.

(16) We are indebted to Messrs. J. L. Roebber, L. J. Winters, B. A. Settle and R. Egan for aid in the preparation of some of the starting materials.

(17) W. W. Hartman and M. R. Brethen, *Org. Syntheses*, **12**, 38 (1932).

(18) W. W. Hartman and R. Phillips, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 464.

(19) C. W. Shoppee, *J. Chem. Soc.*, 696 (1932).

(20) C. D. Gutsche, THIS JOURNAL, **71**, 3513 (1949).

bright yellow needles after five recrystallizations from ethanol; m.p. 145–146°.

Anal. Calcd. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57. Found: C, 60.47; H, 5.38.

Ethyl N-nitroso-N-(4-methoxybenzyl)-carbamate (ID) yielded (a) 64% of **4-methoxybenzyl methyl ether** (IIID), b.p. 57–58° (0.4 mm.), 125° (30 mm.), $n^{25}\text{D}$ 1.5107. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.88; H, 8.02.

(b) 7% of **2-(4′-methoxyphenyl)-cycloheptanone** (IID) obtained, after several recrystallizations from petroleum ether (b.p. 63–69°), as colorless needles, m.p. 57–58° (reported[21] 60°). The **2,4-dinitrophenylhydrazone** of IID was obtained, after several recrystallizations from ethanol–ethyl acetate, as bright yellow plates, m.p. 174–175°. *Anal.* Calcd. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57. Found: C, 60.60; H, 5.64.

Ethyl N-nitroso-N-(2-methylbenzyl)-carbamate (IF), yielded (a) 37% of **2-methylbenzyl methyl ether** (IIIF), b.p. 93° (30 mm.), $n^{25}\text{D}$ 1.5047. *Anal.* Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.10; H, 9.04.

(b) 29% of **2-(2′-methylphenyl)-cycloheptanone** (IIF), b.p. 113° (0.25 mm.), $n^{25}\text{D}$ 1.5348. *Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.29; H, 8.95.

The **2,4-dinitrophenylhydrazone** of IIF was obtained after several recrystallizations from ethanol as bright yellow blades, m.p. 188–189°. *Anal.* Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.80. Found: C, 62.85; H, 5.75.

Ethyl N-nitroso-N-(4-methylbenzyl)-carbamate (IG) yielded (a) 45% of **4-methylbenzyl methyl ether** (IIIG), b.p. 84° (20 mm.), $n^{25}\text{D}$ 1.4990. *Anal.* Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.47; H, 8.75.

(b) 26% of **2-(4′-methylphenyl)-cycloheptanone** (IIG) as feathery, white needles after recrystallization from petroleum ether (b.p. 63–69°), m.p. 57–58°. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 83.12; H, 8.97. Found: C, 83.30; H, 9.03.

The **2,4-dinitrophenylhydrazone** of IIG was obtained, after several recrystallizations from ethanol–ethyl acetate, as glistening, bright orange plates, m.p. 200–201.5°.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.80. Found: C, 63.14; H, 5.91.

Ethyl N-nitroso-N-(2,4,6-trimethylbenzyl)-carbamate (IIH) yielded (a) 62% of **2,4,6-trimethylbenzyl methyl ether** (IIIH), b.p. 56° (0.50 mm.), $n^{25}\text{D}$ 1.5098. *Anal.* Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.47; H, 9.72.

(b) 11% of ethyl N-(2,4,6-trimethylbenzyl)-carbamate, m.p. 109–111°, resulting either from de-nitrosation during the reaction[22] or to incomplete nitrosation in the preparation of IH.

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(21) M. Tiffeneau, P. Weill, J. Gutmann and B. Tchoubar, *Compt. rend.*, **201**, 277 (1935).

(22) F. W. Bollinger, F. N. Hayes and S. Siegel, THIS JOURNAL, **72**-5592 (1950), and **75**, 1729 (1953), obtained ethyl N-cyclohexylcarbamate in 15% yield and ethyl N-cyclopentylcarbamate in 7% yield from the corresponding N-nitroso compounds in methanol in the presence of potassium carbonate.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT OF THE PROCTER & GAMBLE COMPANY]

Mono-α-aminoacyl and Mono-α-dipeptide Triglycerides

BY W. FREDERICK HUBER

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2-α-Aminoacyl-1,3-dilaurins, -dipalmitins, and -distearins have been prepared representing a combination of the acidic constituents of protein and fat in one molecule. They were obtained as the acetate salts by hydrogenation of the corresponding 2-α-azidoacyl glycerides in glacial acetic acid. Hydrolysis of the acetate salts by water-washing yielded free bases with fat-like properties. Treatment of the free bases with an α-azidoacyl chloride, followed by hydrogenation, produced mono-α-dipeptide glycerides. Due to ease of hydrolysis of the aminoacyl ester linkage, pure 1-mono-α-aminoacyl glycerides and di- or tri-α-aminoacyl glycerides were not obtained.

The substitution of α-aminoacyl or polypeptide groups for one or two of the fatty acid groups in a triglyceride was of interest since the products would combine components of protein and fat in one molecule.

Several syntheses of glycerides containing amino acids or both amino acids and fatty acids have been reported.[1] Compounds such as 1-glycyldipalmitin and 1-alanyldistearin have been reported to melt at 215 and 223°, respectively. The compounds were claimed to be soluble in water and insoluble in ligroin or ethyl acetate. These properties seemed unlikely for molecules containing a high percentage of fatty acid groups and the present work confirms this. All the mono-α-aminoacyl glycerides described herein are soluble in petroleum ether, ether or chloroform and insoluble in water. They melt in the range of 30 to 70° and are fat-like in character.

Confirming former workers, efforts to prepare α-aminoacyl glycerides by conventional esterification techniques failed. Similar attempts employing amino acids or their acid chlorides in which the amino group was blocked by an acyl, phthalyl or carbobenzoxy group also failed. 2-Phthalylalanyl-1,3-distearin was prepared, but removal of the phthalyl group could not be accomplished by reaction with hydrazine or phenylhydrazine or by hydrogenation. No 2-carbobenzoxyglycyl-1,3-dipalmitin could be identified in the reaction product from carbobenzoxyglycyl chloride with 1,3-dipalmitin.

The only successful method found for synthesis of aminoacyl glycerides introduced the amino group as the last step by hydrogenation of an azido group. An α-halogeno ester was treated with sodium azide to form an α-azido ester which on saponification formed the α-azido acid. This was converted to the acid chloride with thionyl chloride and reacted with glycerol, a monoglyceride or a diglyceride in chloroform–pyridine solution to form a tri-, di- or mono-α-azidoacyl triglyceride. Hydrogenation of the latter in glacial acetic acid solution converted the azido group to an amino group, liberating nitrogen and producing the corresponding α-aminoacyl glyceride acetate. The acetates, as typical amine salts, are more soluble in polar than non-polar solvents. They are quite unstable to

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(1) (a) A. Fodor and M. Weizmann, *Z. physiol. Chem.*, **154**, 290 (1926); (b) M. Weizmann and L. Haskelberg, *Compt. rend.*, **189**, 104 (1929); (c) M. Weizmann and L. Haskelberg, *Bull. soc. chim.*, **51**, 59 (1932); (d) L. Haskelberg, *Compt. rend.*, **190**, 270 (1930); *Bull. soc. chim.*, **51**, 212 (1932); (e) B. R. Harris, U. S. Patent 2,406,329 (1946).