and then distilled to give, after removal of toluene, 10 g (64%) of a mixture of *cis* (62%) and *trans* (38%) **5**, bp 41° (1 mm), $n^{20}D$ 1.4350. Infrared data and glpc data were in agreement with that of the dihydro rose oxide prepared from **4**.

Acknowledgment.—The authors are grateful to Dr. V. W. Goodlett of these laboratories for interpreting the nmr spectra and to Professor Julia for his kindness in providing the sample of dihydro rose oxide.

Synthesis of β-Substituted Alkylamines *via* Alkylation of N,N-Disubstituted Amides

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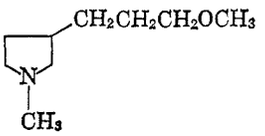
While elucidating the structure of complex rearrangement products from the reaction of N-chloroamines we were confronted with the problem of synthesizing certain 3-substituted 1-methylpyrrolidines. An attractive route to these β-substituted amines appeared to be through lithium aluminum hydride reduction of the corresponding lactams. Lactams of this type were obtainable by base-catalyzed alkylation of the readily available 1-methyl-2-pyrrolidone. While examples of α-C-alkylations of amides in a variety of base–solvent systems can be found in the literature, nearly all such studies have been carried out on α-aryl-substituted amides[2-11] or on amides containing other carbanion-stabilizing substituents on the α-position.[12-16]

Comparison of the anion of an N,N-disubstituted amide (I) and the dianion of a β-diketone (II) shows

I II

that these ions are isoelectronic. It has been amply demonstrated that dianions of type II may be formed by the reaction of β-diketones with sodium amide in liquid ammonia and that these dianions can be subsequently alkylated.[17] The alkylations of unactivated N,N-disubstituted amides under similar conditions appeared quite feasible.

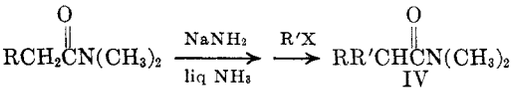
Addition of 1-methyl-2-pyrrolidone to sodium amide in liquid ammonia caused conversion of the pyrrolidone to a monoanion of type I. Alkylation of this anion with 1-bromo-3-methoxypropane followed by reduction of the resulting lactam with lithium aluminum hydride afforded the expected amine, 1-methyl-3-(3-methoxypropyl)pyrrolidine (III), in 42% over-all yield. In view of these results, it appeared that this



III

procedure would be an efficacious route to a variety of β-alkyl-substituted amines. To delineate the usefulness of this synthetic scheme we carried out the typical reactions compiled in Tables I and II.

TABLE I

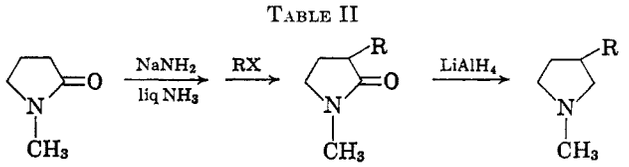


IV

R	R′X	% yield of IV	Bp, °C (mm)	$n^{20}D$
H	CH_3I	68	74 (42)	1.4398[a]
H	CH_3CH_2Br	75	82–83 (37)	1.4421[a]
H	$(CH_3)_2CHBr$	75	72–74 (8)	1.4412
CH_3	CH_3CH_2Br	62	70 (10)	1.4421[b]

[a] Structure was authenticated by comparison with known material. [b] R. Lukeš and J. Langthaler [*Chem. Listy*, **51**, 1869 (1957)] reported bp 76–77° (12 mm), $n^{20}D$ 1.4418.

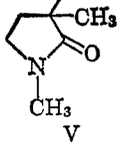
TABLE II



RX	% yield of amine	Bp, °C (mm)	$n^{20}D$	Picrate mp, °C
$CH_3OCH_2CH_2CH_2Br$	42	63–64 (7)	1.4438	127–128
CH_3CH_2Br	41	77 (154)	1.4416	150.5–152.0[a]
$(CH_3CH_2O)_2CHCH_2CH_2Cl$	13	87–88 (1.4)	1.4422	...

[a] R. Lukeš, M. Ferles, and O. Strouf [*Collection Czech. Chem. Commun.*, **24**, 212 (1959)] reported bp 123° (740 mm), $n^{20}D$ 1.4303, picrate mp 152.0–152.5°.

In addition to the monoalkylations listed in Tables I and II, it is also possible to carry out a dialkylation. When 1-methyl-2-pyrrolidone was treated with 2 moles of sodium amide in liquid ammonia followed by the addition of 2 moles of methyl iodide, 1,3,3-trimethyl-2-pyrrolidone (V) was obtained in 45% yield.



V

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The physical constants of this compound agreed with the literature values.[18]

The exploratory reactions listed above indicate that the alkylation of amides in liquid ammonia[19] followed by hydride reduction offers an efficient method of synthesizing β-substituted amines.

Experimental Section

Sodium Amide Solution.—Sodium amide was prepared from sodium and liquid ammonia using ferric chloride as the catalyst. The system was equipped with a constant-pressure dropping funnel and the reaction vessel was kept free of air.

Alkylation of N,N-Disubstituted Acyclic Amides. General Procedure.—To a stirred suspension of sodium amide in liquid ammonia was added an equivalent amount of the amide. After stirring for 20 min, an equivalent amount of alkyl halide was added dropwise with stirring over *ca.* a 0.5-hr period. The reaction mixture was stirred for 1 hr and 150 ml of ether was added. The ammonia was allowed to evaporate. From this point alternate procedures were used depending on the crystallinity of the precipitated salts.

Procedure A.—The highly crystalline salts were filtered off and rinsed thoroughly with ether. After drying the combined filtrate and rinses over anhydrous magnesium sulfate, the desiccant was filtered off and the filtrate was concentrated on a steam bath. The residue was then distilled through a spinning-band column having 28 theoretical plates. The purity of the distillate was ascertained by glpc using a 5-ft column of 5% SE-30 on Fluoropak at 120°.

Procedure B.—The ethereal layer was decanted from the salt slurry and saved. The walls of the reaction flask were rinsed with a few milliliters of 95% ethanol to destroy any residual sodium. The salts were than taken up in water and either manual'y extracted at least six times or continuously extracted for 48 to 54 hr with ether. The combined ethereal extracts were dr'ed over anhydrous magnesium sulfate and worked up as in procedure A.

Preparation of 3-Substituted 1-Methylpyrrolidines. General Procedure.—The alkylation of 1-methyl-2-pyrrolidone was carried out as described above for acyclic amides. The crude reaction mixture contained some 1-methyl-2-pyrrolidone along with the alkylated product (as determined by glpc using a 10-ft column of 12% Carbowax 20M on Fluoropak at 170°). This mixture was taken up in anhydrous ether and added dropwise with stirring to a slight excess of lithium aluminum hydride in anhydrous ether. After stirring for 14 hr at room temperature, the reaction was hydrolyzed, the salts were filtered off, and the filtrate was dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a steam bath. Depending upon the relative boiling points of 1-methylpyrrolidine (from reduction of the starting lactam) and the product, the residue was either distilled through the spinning-band column referred to above or through a short Vigreux column. The two heretofore unknown amines prepared by this method were analyzed: **1-methyl-3-(3-methoxypropyl)pyrrolidine** (*Anal.* Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.31; H, 12.20; N, 8.95.); **1-methyl-3-(3,3-diethoxypropyl)pyrrolidine** (*Anal.* Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.72; H, 11.64; N, 6.48.).

1,3,3-Trimethyl-2-pyrrolidone.—To a stirred suspension of sodium amide in liquid ammonia, prepared from 9.2 g (0.4 g-atom) of sodium metal as described in the general procedure, was added 19.8 g (0.2 mole) of 1-methyl-2-pyrrolidone. After stirring for 20 min, 56.8 g (0.4 mole) of methyl iodide was added dropwise with stirring over a period of 1 hr. Stirring was continued for an additional 1 hr. About 150 ml of ether was added and the ammonia was allowed to evaporate. After work-up according to procedure B, 11.27 g (45.4%) of pure 1,3,3-trimethyl-2-pyrrolidone was obtained, bp 72–73° (20 mm), $n^{20}D$ 1.4567 [lit.[18] bp 87° (20 mm), $n^{20}D$ 1.4568]. The nmr spectrum of the compound showed the following integrated intensities and multiplicities: τ 6.74, 2 H (triplet, J = 6.8 cps); 7.27, 3 H (singlet); 8.17, 2 H (triplet, J = 6.8 cps); and 8.75, 6 H (singlet). This spectral data was consistent with the assigned structure.

Acknowledgment.—The authors are indebted to the National Cancer Institute for Public Health Service Grant CA-07110-1, which partially supported this investigation.

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(19) We have recently learned that a similar alkylation study has been carried out in benzene and toluene by H. L. Needles and R. E. Whitfield, Western Regional Research Laboratory, Albany, Calif. We wish to thank these authors for informing us of their results prior to publication.

The Reformatsky Reaction. I. Condensation of Ketones and *t*-Butyl Bromoacetate by Magnesium

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It was discovered by Sisido and co-workers[1] that the aldol-type condensation of esters with ketones in the presence of diethylaminomagnesium bromide to form β-hydroxy esters could best be carried out by the use of *t*-butyl esters. Similar condensation was effected also by Hauser and co-workers[2] with lithium amide or a mixture of sodium amide and zinc chloride as a condensing agent. The ester components used by these authors were again the *t*-butyl esters. It has similarly been observed by Hauser and co-workers[3-5] that ethyl acetate can be condensed satisfactorily with various aldehydes and ketones by the improved procedure.

The mechanism of these condensations appears to be very close to the Reformatsky reaction.[6] When the zinc is replaced by the more reactive magnesium, the halomagnesium enolate attacks also the carbonyl carbon of the ester to form β-keto esters.[7] Such a condensation occurs naturally to some extent also in the presence of zinc, causing the drop in yields of the β-hydroxy esters. The above-mentioned observations suggest the use of *t*-butyl halo esters, which may be expected to retard the possible self-condensation of the α-halo esters.[8]

It has now been found that the Reformatsky reaction can be carried out conveniently by magnesium with improved yield. Thus, to a mixture of ether and magnesium was added a solution of *t*-butyl bromoacetate and a ketone in ether, and the reaction mixture was decomposed with dilute acidic solution after refluxing was continued for about 1 hr. The experimental results are summarized in Table I. The condensation products from benzalacetone or benzalacetophenone were not isolated; they were converted to the α,β-unsaturated acid by alkaline hydrolysis in an over-

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