[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

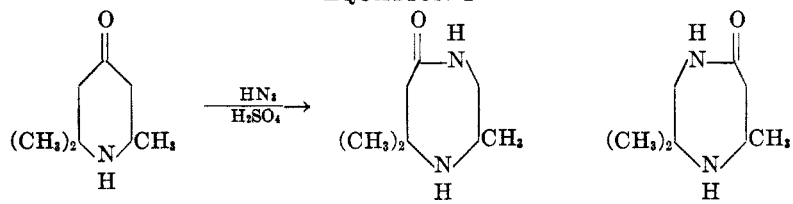
THE SCHMIDT REACTION WITH 2,2,6-TRIMETHYL- AND 1,3-DIMETHYL-4-PIPERIDONES[1]

S. C. DICKERMAN AND E. J. MORICONI[2]

Received September 8, 1954

In a previous communication (1) it was demonstrated that 4-piperidones undergo conversion during the Schmidt reaction to 5-homopiperazinones. This communication reports the application of this reaction to 2,2,6-trimethyl-4-piperidone (I) and 1,3-dimethyl-4-piperidone (VI).

EQUATION I



I II II′

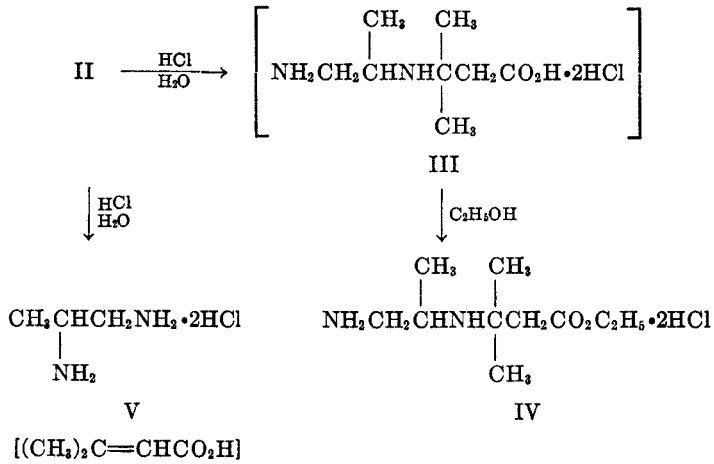
When I was treated with hydrazoic and sulfuric acids 2,7,7-trimethyl-5-homopiperazinone (II) was isolated. Equation I illustrates this reaction; the structure of the isomeric homopiperazinone II′ not isolated is included for comparison. The cyclic amide II was characterized by the preparation of a neutral nitrosamine derivative and degradation to 1,2-diaminopropane dihydrochloride (V). This reaction and the complete pattern of degradation is illustrated in Equation II. The diamine dihydrochloride V was converted to a dibenzoyl derivative which was shown to be identical with an authentic sample. No attempt was made to isolate 3-methyl-2-butenoic acid. Under less severe hydrolytic conditions the diamino acid III was isolated. This diamino acid dihydrochloride III was obtained as an oil and was converted to the crystalline ester dihydrochloride IV.

A second investigation was carried out with 1,3-dimethyl-4-piperidone (VI) which, on treatment with hydrazoic and sulfuric acids, produced 1,3-dimethyl-5-homopiperazinone (VII). Equation III illustrates this reaction; again the isomeric homopiperazinone VII′, that was not isolated, is included for comparison. The structure of VII was established by hydrolysis to 1-methylamino-2-aminopropane dihydrochloride, m.p. 175–176° (dec.), which appears to have been previously unreported. The isomeric homopiperazinone VII′ would have yielded N-methylethylenediamine dihydrochloride which has been reported (2) to melt at 130–132°. The diamine was characterized by conversion to a dibenzoyl derivative.

[1] An abstract of a thesis submitted by E. J. Moriconi to the faculty of New York University in partial fulfillment of the requirements for the degree of Master of Science, October 1948.

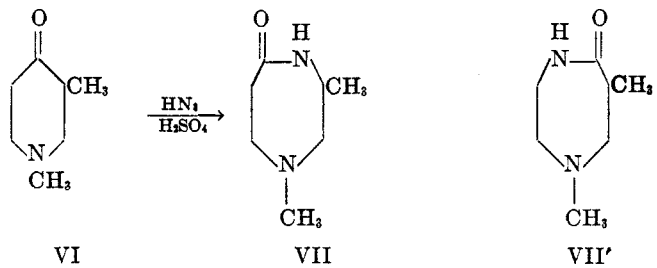
[2] Present address, Department of Chemistry, Fordham University.

EQUATION II



The formation of 1,3-dimethyl-5-homopiperazinone (VII) in apparently larger amount than its isomer VII′ is not surprising and can be interpreted in terms of the steric effect of the *alpha*-methyl group. Smith (3) has suggested that the Schmidt reaction proceeds by a mechanism which resembles the Beckmann rearrangement and like the latter is largely dependent on steric factors. Thus it is of some interest to compare our results with those reported for the Beckmann rearrangement. Unfortunately piperidone oximes do not undergo this reaction in good yield (1) and it is necessary to make the comparison with identically substituted cyclohexanone oximes. Subject to the limitations of this analogy, our results are in agreement with Ungnade and McLaren's observation (4) that 2-methylcyclohexanone oxime undergoes rearrangement *via* migration of the substituted carbon atom.

EQUATION III



There does not seem to be any such obvious explanation for the preferred formation of homopiperazinone II at the expense of II′. A simple steric interpretation will not suffice since the substituents are in positions *beta* to the carbonyl group. Comparison with the Beckmann rearrangement reveals that 3,3,5-trimethylcyclohexanone oxime has been reported (5, 6) to give a mixture of amides. While our work may indicate a greater predominance of one structural isomer it does not preclude the presence of the other isomer in the crude product.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses by E. J. Moriconi.

2,7,7-Trimethyl-5-homopiperazinone (II) *and hydrochloride.* A chloroform (10 ml.) suspension of 6.69 g. (0.03 mole) of 2,2,6-trimethyl-4-piperidone acid oxalate (I) (7) was cooled in an ice-bath and stirred as conc'd sulfuric acid (24 ml.) was added dropwise. This mixture then was vigorously stirred as 3.90 g. (0.06 mole) of solid sodium azide was added over a period of one-half hour. After the vigorous reaction had subsided the mixture was stirred for an additional half-hour and while still in the ice-bath was neutralized with sodium hydroxide solution. The syrupy mixture was then transferred to a 500-ml. Erlenmeyer flask with the aid of 50 ml. of water and the whole was saturated with solid potassium carbonate. The resulting paste was extracted with eight 50-ml. portions of chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered, and the chloroform removed under reduced pressure to yield 4.20 g. (90%) of light brown solid, m.p. 120–130°. Several recrystallizations from dry benzene afforded 3.03 g. (64%) of II as colorless needles, m.p. 135.5–136.5°.

Anal. Calc'd for $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9.

Found: C, 61.4; H, 10.4; N, 17.7.

The *hydrochloride* of II was prepared in absolute ethanol with ethanolic hydrogen chloride and crystallized by the addition of absolute ethyl ether, m.p. 250–252° (dec.).

Anal. Calc'd for $C_8H_{17}ClN_2O$: Cl, 18.4; N, 14.5.

Found: Cl, 18.7; N, 14.2.

1-Nitroso-2,7,7-trimethyl-5-homopiperazinone. A portion of II was converted to a nitroso derivative in the usual manner. This derivative was obtained as pale green microcrystals from benzene, m.p. 163–164°. The Liebermann test was positive.

Anal. Calc'd for $C_8H_{15}N_3O_2$: N, 22.7. Found: N, 22.5.

Degradation of II. *Isolation of 1,2-propanediamine dihydrochloride* (V). The homopiperazinone II (0.940 g.) was dissolved in 10 ml. of 20% hydrochloric acid and the solution was refluxed for 70 hours. Evaporation of the water and acid gave a yellow pasty residue which was dissolved in hot absolute ethanol and crystallized by the addition of absolute ether. One recrystallization from an ethanol-ether mixture yielded 0.408 g. (46%) of 1,2-propanediamine dihydrochloride (V) as white plates, m.p. 222–223° (dec.); reported (8) 220°. This diamine dihydrochloride V was converted to a dibenzoyl derivative of m.p. 194–195°, reported (8) 192–193°. A mixture of this derivative and an authentic sample of 1,2-dibenzamidopropane[3] melted at 194–195°.

Hydrolysis of II. *Preparation of ethyl 3-(2'-aminoisopropylamino)-3-methylbutanoate dihydrochloride* (IV). A solution of 1.20 g. (7 millimoles) of II in 15 ml. of 10% hydrochloric acid was refluxed for two hours. Evaporation of the solution on a steam-bath with a stream of dry air gave a viscous yellow oil, the amino acid dihydrochloride, which could not be crystallized. Esterification was effected by refluxing with 10 ml. of absolute ethanol for a period of one hour. The alcohol solution then was decolorized with charcoal, filtered, concentrated to a volume of 5 ml., and the ester IV crystallized by the addition of absolute ether. The yield amounted to 1.10 g. (52%), m.p. 168–170° (dec.). Recrystallization from a mixture of the same solvents gave IV as colorless microcrystals of m.p. 170–171° (dec.).

Anal. Calc'd for $C_{10}H_{24}Cl_2N_2O_2$: C, 43.6; H, 8.8; N, 10.2.

Found: C, 43.5; H, 9.1; N, 10.3.

A sample of IV was degraded in the manner previously described for II and 1,2-propanediamine dihydrochloride was isolated in about the same yield.

1,3-Dimethyl-5-homopiperazinone (VII), *hydrochloride and picrate.* 1,3-Dimethyl-4-piperidone hydrochloride (VI), prepared as described by Howton (9), was converted to VII by the procedure previously reported for the synthesis of II. From 2.75 g. of piperidone

[3] Prepared from a research sample of 1,2-diaminopropane generously supplied by Carbide and Carbon Chemicals Co.

there was obtained 1.60 g. (67%) of crude 1,3-dimethyl-5-homopiperazinone (VII) of m.p. 110–120°. Two recrystallizations from dry benzene gave 0.905 g. (38%) of VII as colorless needles, m.p. 133–134°.

Anal. Calc'd for $C_7H_{14}N_2O$: C, 59.1; H, 9.9; N, 19.7.
Found: C, 59.0; H, 9.6; N, 19.6.

The *hydrochloride* of VII was prepared in the usual manner and recrystallized from absolute ethanol-ether as colorless hygroscopic needles of m.p. 234–235° (dec.).

Anal. Calc'd for $C_7H_{15}ClN_2O$: Cl, 19.9; N, 15.7.
Found: Cl, 19.7; N, 15.8.

The *picrate* of VII was obtained as a yellow powder of m.p. 220–223° (dec.). Analysis for $C_{12}H_{17}N_5O_8$.

Degradation of VII. *Isolation of 2-amino-1-methylaminopropane dihydrochloride.* The homopiperazinone VII (0.685 g.) was dissolved in 10 ml. of 20% hydrochloric acid and the solution refluxed for 72 hours. The acid solution was concentrated to yield a yellow oil which was dissolved in hot absolute ethanol. The dihydrochloride was crystallized from this solution by the addition of absolute ether. The yield amounted to 0.375 g. (49%), m.p. 170–175°. Two recrystallizations from the same solvents afforded 2-amino-1-methylaminopropane dihydrochloride as hygroscopic needles of m.p. 175–176° (dec.).

Anal. Calc'd for $C_4H_{14}Cl_2N_2$: C, 29.8; H, 8.8; N, 17.4.
Found: C, 30.0; H, 8.9; N, 17.1.

A sample of 2-amino-1-methylaminopropane dihydrochloride was converted to the dibenzoyl derivative by the usual method. After recrystallization from an ethanol-water mixture N,N′-dibenzoyl-2-amino-1-methylaminopropane was obtained as colorless platelets of m.p. 138–138.5°.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: N, 9.4. Found: N, 9.3.

SUMMARY

Two unsymmetrically substituted 4-piperidones have been subjected to the Schmidt reaction with the following results: 2,7,7-trimethyl-5-homopiperazinone was obtained from 2,2,6-trimethyl-4-piperidone while 1,3-dimethyl-5-homopiperazinone was produced from 1,3-dimethyl-4-piperidone. The structure of each homopiperazinones was established by degradation to diamines one of which, 1-methylamino-2-aminopropane, was hitherto unknown.

NEW YORK 53, N. Y.

REFERENCES

(1) DICKERMAN AND LINDWALL, *J. Org. Chem.*, **14**, 530 (1949).
(2) JOHNSON AND BAILEY, *J. Am. Chem. Soc.*, **38**, 2141 (1916).
(3) SMITH, *J. Am. Chem. Soc.*, **70**, 320 (1948).
(4) UNGNADE AND MCLAREN, *J. Org. Chem.*, **10**, 29 (1945).
(5) WALLACH, *Ann.*, **346**, 256 (1906).
(6) SNIDER AND MORRIS, U. S. Patent 2,462,008; *Chem. Abstr.*, **43**, 3450 (1949).
(7) HARRIES, *Ber.*, **29**, 522 (1896).
(8) STRACHE, *Ber.*, **21**, 2359 (1888).
(9) HOWTON, *J. Org. Chem.*, **10**, 277 (1945).