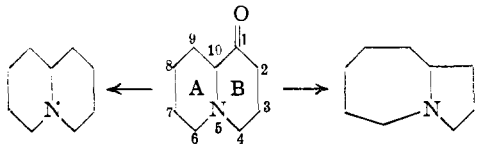
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Rearrangement of α-Aminoketones During Clemmensen Reduction. I. Bicyclic Compounds Containing a Bridge-head Nitrogen[1]

BY NELSON J. LEONARD AND WILLIAM C. WILDMAN

The Clemmensen reduction of 1-ketoquinolizidine (I) leads not to the normal product, quinolizidine (II),[2] but to the rearrangement product, 1-azabicyclo[5.3.0]decane (III).[3] We have now established that this reductive rearrangement proceeds with ketone-ring (B) contraction.

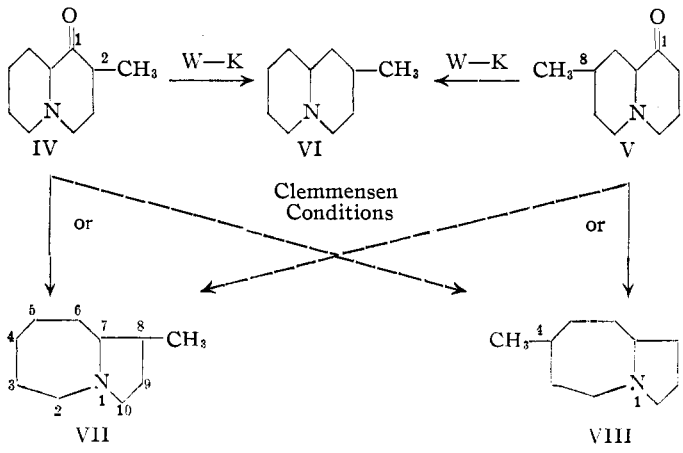


II I III

Quinolizidine (II),[4] the parent nucleus of the *Lupin* alkaloids, was first synthesized by Clemo, Ramage and Raper in 1932.[5] The compound was also synthesized satisfactorily in the same laboratory[2] by the Clemmensen reduction of 2-ketoquinolizidine and by the Wolff–Kishner reduction of 1-ketoquinolizidine (I). However, when the Clemmensen method was applied to I, an isomer of II was obtained, the structure of which was unknown until proved through an unequivocal synthesis by Prelog and Seiwerth[3] to be 1-azabicyclo[5.3.0]decane (III). No clearly outlined mechanism for this unusual rearrangement has been proposed, but Prelog and Seiwerth suggested that the first step might be a cleavage of the α–C–N bond in the acid medium, followed by an intramolecular condensation of the secondary amino group with the carbonyl group and reduction to give the new ring system. The work of Cromwell[6] indicates that α-aminoketones are not as readily cleaved as β-aminoketones in acid medium. Nevertheless, if cleavage is involved as the initial step in the rearrangement, it is conceivable that α,β-unsaturation might develop. The secondary amine could then add intramolecularly in a 1,4-manner to the unsaturated ketone. In other words, the conversion of I to III does not indicate whether it is ring A or ring B which contracts from a six to a five-membered ring. A logical way to begin the study of the mechanism of the rearrangement is to learn which ring contracts and which expands.

The "labelling" of either ring with a methyl group provides an attractive means of following contraction or expansion. Clemo and his coworkers have provided the model compounds, for they carried out Clemmensen reductions of 1-keto-2-methylquinolizidine (IV)[7] and 1-keto-8-methylquinolizidine (V).[8] The products of Clemmensen reduction were not identical with each other and were not identical with the normal (Wolff–Kishner) reduction product of each: 2-methylquinolizidine (VI).[9]

The Clemmensen reduction products are therefore represented as VII and VIII, but the question as to which rearranged amine resulted from which aminoketone could not be decided until the amines were synthesized by an unequivocal method. We have now completed unequivocal syntheses of VII and VIII, and it is the comparison of these amines with the Clemmensen reduction products of IV and V which enables us to state that the ketonic ring (B) contracts. In brief, identical physical properties were exhibited by the derivatives of 8-methyl-1-azabicyclo[5.3.0]decane (VII) (picrate, m. p. 181–182°; picrolonate, m. p. 189–190°) and the Clemmensen reduction product of IV (picrate, m. p. 182°; picrolonate, m. p. 189°)[7]; by the derivatives of 4-methyl-1-azabicyclo[5.3.0]decane (VIII) (picrate, m. p. 189°; picrolonate, m. p. 138–139°) and the Clemmensen reduction product of V (picrate, m. p. 189°; picrolonate, m. p. 138°).[8] The established course of



IV VI V VII VIII

(1) Supported in part by a grant from the Research Board of the University of Illinois.

(2) Clemo, Metcalfe and Raper, *J. Chem. Soc.*, 1429 (1936).

(3) Prelog and Seiwerth, *Ber.*, **72**, 1638 (1939).

(4) Known alternatively as norlupinane, octahydropyridocoline, and 1-azabicyclo[4.4.0]decane.

(5) Clemo, Ramage and Raper, *J. Chem. Soc.*, 2959 (1932).

(6) Cromwell, *Chem. Rev.*, **38**, 83 (1946), and primary references.

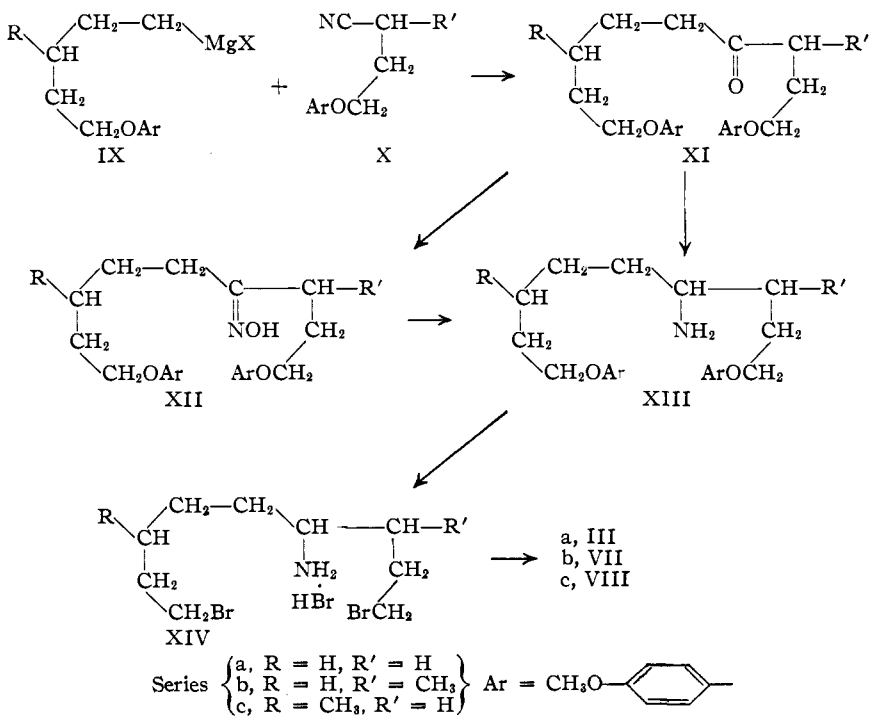
(7) Clemo and Metcalfe, *J. Chem. Soc.* 1518 (1937).

(8) Clemo, Cook and Raper, *ibid.*, 1183 (1938).

(9) The product of Wolff–Kishner reduction of IV was described as 2-methyloctahydropyridocoline (picrate, m. p. 158°; picrolonate, m. p. 219°)[7]; that from V, as 8-methyloctahydropyridocoline (picrate, m. p. 150°; picrolonate, m. p. 197°).[8] Both products should be named 2-methyloctahydropyridocoline (or 2-methylquinolizidine). Even if they were not actually identical, they could only be different racemates represented by the same structure (VI).

the Clemmensen reduction is thus indicated by the unbroken arrows in the accompanying diagram (IV → VII and V → VIII).

Unequivocal methods of synthesis of VII and VIII were realized by applying certain modifications to the general method which Prelog and his co-workers devised for the preparation of bicyclic compounds containing a bridge-head nitrogen.[3,10,11] Our modified method was checked by a "control" run: the synthesis of the known compound, 1-azabicyclo[5.3.0]decane (III), through the intermediates IXa, Xa, XIa, XIIa, XIIIa, and XIVa. The methyl-substituted products VII and VIII were then prepared by the similar reaction series b and c. The use of the terminal aryloxy group in the intermediates (IX, X, XI, and XIII) was suggested by our desire to work with crystalline and easily separable compounds. The utilization of the *p*-methoxyphenoxy group specifically was guided by the finding of Ziegler and his coworkers[12] that certain *p*-methoxyphenyl ethers were cleaved by acid more readily than the analogous phenyl ethers. The use of the *p*-methoxyphenoxy group insured facile acid cleavage of XIII to XIV.



The first step in the general procedure employed for the synthesis of III, VII and VIII was the Grignard reaction. The halide precursors of the Grignard reagents IXa and IXc were made by condensation of hydroquinone monomethyl ether with 1,5-dichloropentane and 1,5-dibromo-3-methylpentane,[13] respectively. The nitriles Xa and Xb were made by methods previously described for the phenoxy analogs. The reaction between the Grignard reagents (IX) and the nitriles (X) proceeded normally, but special precautions were necessary in the hydrolysis and isolation to insure the maximum yield of each ketone, 1,9-bis-(*p*-methoxyphenoxy)-4-nonanone (XIa), 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-4-nonanone (XIb), and 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-6-nonanone (XIc). Oximes (XII) were formed from each ketone, and the oximes could be reduced with sodium and ethanol to the corresponding amines (XIII). However, the conversion of the ketones (XI) to the amines (XIII) was accomplished more efficiently by hydrogenation in liquid ammonia over Raney nickel catalyst at high temperature and pressure. 4-Amino-1,9-bis-(*p*-methoxyphenoxy)-nonane (XIIIa) was obtained in crystalline form without difficulty. Although the other two amines (XIIIb and XIIIc) were not readily crystallizable, suitable crystalline derivatives were found in the hydrochloride monohydrate of 4-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIb) and in the half ammonium oxalate salt of 6-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIc). No attempt was made to isolate the α,ω-dibromoamine hydrobromides (XIV) which were obtained by hydrobromic acid cleavage of XIII, although the quantitative recovery of hydroquinone in a trial run indicated that cleavage was proceeding satisfactorily. The crude α,ω-dibromoamine hydrobromides (XIV) were converted to the 1-azabicyclo[5.3.0]decanes (III, VII, VIII) by intramolecular dialkylation of the primary amine group in dilute aqueous sodium hydroxide. The final products (III, VII, VIII) were characterized by the formation of suitable derivatives. Although diastereoisomeric racemates might have been expected from both 8-methyl-1-azabicyclo[5.3.0]-decane (VII) and 4-methyl-1-azabicyclo[5.3.0]-decane (VIII), single derivatives were isolated in every case.

With the establishment of the fact that the ketone ring contracts during the Clemmensen reduction of the 1-ketoquinolizidines (I, IV, V), it be-

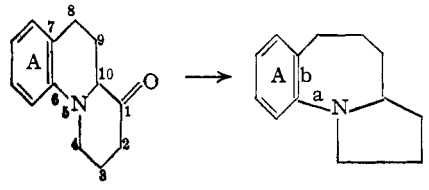
(10) Prelog and Bozicevic, *Ber.*, **72**, 1103 (1939).

(11) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 531 (1944).

(12) (a) Ziegler and Weber, *Ber.*, **70**, 1275 (1937); (b) Ziegler, Weber and Gellert, *ibid.*, **75**, 1715 (1942).

(13) Leonard and Wicks, THIS JOURNAL, **68**, 2402 (1946).

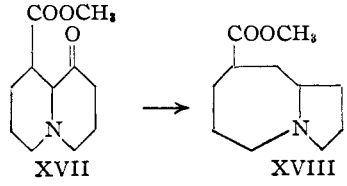
comes possible to assign correct structures to the Clemmensen reduction products of several analogous compounds investigated by Clemo and his co-workers. The product of Clemmensen reduction (which differed from the normal or Wolff–Kishner product)[14] of 1-keto-6,7-benzoquinolizidine (XV)[15] therefore has the structure: benzo[b]-1-azabicyclo[5.3.0]decane (XVI). The product of Clemmensen reduction (which differed from the Wolff–Kishner product)[14] of 1-keto-6,7-hexa-



XV XVI

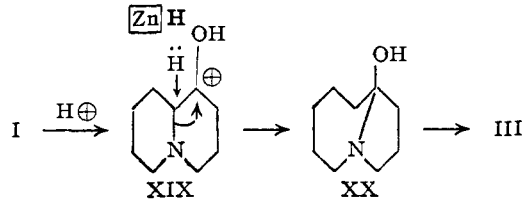
(a, ring A fully saturated)

hydrobenzoquinolizidine (XVa)[16] is therefore hexahydrobenzo[b]-1-azabicyclo[5.3.0]decane (XVIa). The product of Clemmensen reduction of methyl 9-ketoquinolizidine-1-carboxylate (XVII) (which was degraded by Clemo, Ramage and Raper[17] to 1-azabicyclo[5.3.0]decane (III)) must possess the structure: methyl 1-azabicyclo[5.3.0]-decane-5-carboxylate (XVIII).



XVII XVIII

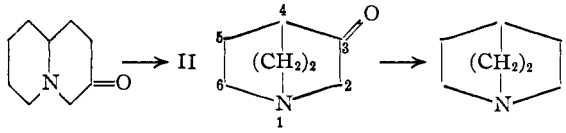
These examples serve as illustrations of a rearrangement which appears to be general in scope. The products of the rearrangement can be accounted for by an elaboration of the suggestion of Prelog and Seiwerth[3]



XIX XX

The first step would involve the migration of the R_2N- group to the geometrically-fixed, adjacent carbonium carbon (formed from the carbonyl group in acid solution),[18a] with the subsequent or simultaneous attack of hydrogen at the newly-formed carbonium ion of the α-carbon (XIX → XX). Reductions of the type represented by the second step, conversion of XX to III, appear to occur readily.[18b,c]

The limitations, the confining structural features of the α-substituted ketones, and a study of the proposed mechanism of the rearrangement constitute the subject matter of succeeding articles. At present, it is important to mention the fact that rearrangement was found not to occur in the Clemmensen reduction of at least two related α-aminoketones of the bicyclic, bridge-head-nitrogen type. Clemmensen reduction of 3-ketoquinolizidine (XXI) gave a low yield of the normal product, quinolizidine (II),[19a] and similar reduction of 3-ketoquinuclidine (XXII) gave quinuclidine (XXIII).[19b]



XXI XXII XXIII

Clemmensen reduction of β-aminoketones of the bicyclic, bridge-head-nitrogen type invariably produced unrearranged products.[2,20]

Experimental[21,22]

Halides

1-Bromo-3-(*p*-methoxyphenoxy)-propane.—The procedure used for the condensation of hydroquinone monomethyl ether with α,ω-dihaloalkanes was based on the method of Ziegler and Weber[12a] for phenoxyalkyl halides. The yields were similar for all compounds synthesized in this manner. The following synthesis is representative of the series. A solution of 28 g. (0.5 mole) of potassium hydroxide in 350 ml. of methanol was added over a period of one hour to a stirred solution of 62 g. (0.5 mole) of hydroquinone monomethyl ether (Tennessee Eastman Corporation) and 400 g. (1.98 moles) of 1,3-dibromopropane at reflux temperature. The reaction mixture was boiled under reflux until the solution was neutral to litmus (about six hours). The solution was cooled, and sufficient water was added to dissolve the potassium bromide. The non-aqueous layer was washed twice with water, dried over magnesium sulfate, and distilled. Three hundred grams of 1,3-dibromopropane was recovered. The 1-bromo-3-(*p*-methoxyphenoxy)-propane was obtained as a light yellow oil, b. p. 120–130° (1 mm.); yield, 75 g. (61.5%). The crude product was redistilled for analysis, b. p. 126–127° (1 mm.); $n^{20}D$ 1.5463; d^{20}_4 1.3788.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.34; MR_D 55.85. Found: C, 49.25; H, 5.47; MR_D 56.31.

1-Bromo-3-methyl-5-(*p*-methoxyphenoxy)-pentane.—B. p. 133–134° (0.5 mm.); $n^{20}D$ 1.5311; d^{20}_4 1.2829.

Anal. Calcd. for $C_{13}H_{19}O_2Br$: C, 54.37; H, 6.66; MR_D 68.69. Found: C, 54.46; H, 6.93; MR_D 69.27.

(14) Clemo, Cook and Raper, *J. Chem. Soc.*, 1318 (1938).

(15) Alternative name: 1-keto-6,7-benzo-1,2,3,4,8,9-hexahydropyridocoline.[14]

(16) Alternative name: 1-ketododecahydro-6,7-benzopyridocoline.[14]

(17) Clemo, Ramage and Raper, *J. Chem. Soc.*, 3190 (1931).

(18) (a) Whitmore, *Chem. Eng. News*, **26**, 668 (1948); (b) Alexander and Wildman, THIS JOURNAL, **70**, 1187 (1948); (c) Bunnett and Marks, *ibid.*, **71**, 1587 (1949).

(19) (a) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935); (b) Clemo and Metcalfe, *ibid.*, 1989 (1937).

(20) Lions and Willison, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 240 (1940).

(21) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.

(22) The calculated molecular refractivities do not take into account exaltations due to the benzene ring and the *para*-methoxyl group.

1-Chloro-5-(*p*-methoxyphenoxy)-pentane.—B. p. 153–154° (2 mm.); $n^{20}D$ 1.5209; d^{20}_4 1.1107.

Anal. Calcd. for $C_{12}H_{17}O_2Cl$: C, 63.01; H, 7.49; *MR*D 62.18. Found: C, 63.14; H, 7.24; *MR*D 62.68.

1-Bromo-2-(*p*-methoxyphenoxy)-ethane.—In order to obtain this compound pure, it was necessary to depart from the procedure described above in one important particular. The organic layer was washed with 5% sodium hydroxide and then twice with water before the drying and distilling operations. The 1-bromo-2-(*p*-methoxyphenoxy)-ethane was obtained as a light yellow oil, b. p. 105–108° (2 mm.), which solidified upon standing. Recrystallization from ethanol gave colorless platelets, m. p. 51.5–52.5°.

Anal. Calcd. for $C_9H_{11}O_2Br$: C, 46.77; H, 4.79. Found: C, 46.82; H, 4.82.

Nitriles

Ethyl α-Cyano-γ-(*p*-methoxyphenoxy)-butyrate.—The ester was prepared by the procedure of Robinson and Watt[23] for the condensation of phenoxyethyl bromide with ethyl cyanoacetate, with the exception that twice the recommended pressure was employed. A mixture of 92.4 g. (0.40 mole) of 1-bromo-2-(*p*-methoxyphenoxy)-ethane, 56.0 g. (0.40 mole) of anhydrous potassium carbonate, and 226 g. (2.0 moles) of ethyl cyanoacetate was heated under reflux at 130° and 120 mm. for twenty-two hours. The reaction mixture was cooled, and sufficient water was added to dissolve the inorganic salts. The ester layer was washed with water until neutral and was fractionally distilled. The first fraction contained 116 g. of unreacted ethyl cyanoacetate, b. p. 95–98° (14 mm.). The second fraction consisted mainly of unreacted 1-bromo-2-(*p*-methoxyphenoxy)-ethane, 37 g., b. p. 80–135° (1 mm.). The condensation product boiled at 166–170° (1 mm.); yield 51.0 g. (81% based on unrecovered halide). The crude product was redistilled for analysis, b. p. 169–170° (1 mm.); $n^{20}D$ 1.5083; d^{20}_4 1.1431.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32; *MR*D 67.95. Found: C, 64.14; H, 6.57; N, 5.48; *MR*D 68.66.

Ethyl α-Cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate.—The sodium derivative of ethyl-α-cyano-γ-(*p*-methoxyphenoxy)-butyrate was prepared by the addition of 52.6 g. (0.20 mole) of ethyl α-cyano-γ-(*p*-methoxyphenoxy)-butyrate to an ethanolic solution of 0.2 mole of sodium ethoxide from the reaction of 4.6 g. (0.20 mole) of sodium with 200 ml. of absolute ethanol. Eighty-five grams (0.60 mole) of methyl iodide was added over a period of one-half hour at reflux temperature to the stirred solution of the sodio-derivative. The mixture was refluxed for five hours. The ethanol and methyl iodide were removed by distillation. The oily residue was washed with water, and the water layer was extracted twice with ether. The combined ester and ether layers were dried over magnesium sulfate and distilled. The ethyl α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate was obtained as a colorless liquid, b. p. 162–163° (0.5 mm.); $n^{20}D$ 1.5024; d^{20}_4 1.1413; yield 50.5 g. (91%).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05; *MR*D 72.77. Found: C, 65.06; H, 6.79; N, 4.91; *MR*D 72.13.

α-Cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric Acid.—A solution of 45 g. (0.162 mole) of ethyl α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate in 100 ml. of ethanol was treated with one equivalent of 30% aqueous potassium hydroxide and allowed to stand at room temperature for six hours. The mixture was neutralized with one equivalent of 6 *N* hydrochloric acid. The cyano acid was separated, and the aqueous solution was extracted twice with ether. The cyano acid and ether extracts were combined and dried over magnesium sulfate. The ether was removed under reduced pressure. The residual yellow oil was caused to crystallize by standing twelve hours at 0°. The α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric acid was isolated by filtration. The filtrate (15.1 g.) was composed largely of unreacted ester which was resaponified and worked up in the same manner. The total yield of the crude cyano acid was 36 g. (89.3%). For analysis a small portion was recrystallized twice from hot water to yield white needles, m. p. 80–81°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.86; H, 6.14; N, 5.64.

1-(*p*-Methoxyphenoxy)-3-cyanobutane (Xb).—Sixty grams (0.24 mole) of crude α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric acid was heated at 200° for two hours. The liquid was cooled, washed once with 5% sodium carbonate solution and once with water, dried over magnesium sulfate, and distilled. The 1-(*p*-methoxyphenoxy)-3-cyanobutane was obtained as a colorless liquid, b. p. 146–149° (1.3 mm.); yield 37 g. (75%). The nitrile solidified upon standing. For analysis a small portion was recrystallized from ether as colorless platelets, m. p. 46–47°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.38; H, 7.53; N, 6.64.

1-Cyano-3-(*p*-methoxyphenoxy)-propane (Xa).—The following procedure was that employed by von Braun[24] for the preparation of the phenoxy homolog. A solution of 77.0 g. (0.314 mole) of 1-bromo-3-(*p*-methoxyphenoxy)-propane and 65 g. (1.0 mole) of potassium cyanide in 520 ml. of 70% ethanol was boiled under reflux for six hours. The ethanol was removed by distillation. The nitrile was dissolved in 100 ml. of ether, washed twice with water, and dried over anhydrous magnesium sulfate. The nitrile boiled at 150–153° (1 mm.); yield 45 g. (75%). The nitrile solidified upon standing. Recrystallization of a small portion from ethanol yielded colorless platelets, m. p. 37–38°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 69.10; H, 6.85; N, 7.33. Found: C, 69.24; H, 6.70; N, 7.45.

Ketones

1,9-bis-(*p*-Methoxyphenoxy)-4-nonanone (XIa).—A solution of 8 g. (0.042 mole) of 1-cyano-3-(*p*-methoxyphenoxy)-propane in 35 ml. of anhydrous ether was added with stirring to a Grignard reagent prepared from 1.25 g. (0.052 mole) of magnesium, 11.4 g. (0.05 mole) of 1-chloro-5-(*p*-methoxyphenoxy)-pentane, and 35 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then was decomposed at 0° by the slow addition of 80 ml. of 1.2 *N* hydrochloric acid. The crude ketone was isolated by filtration. The ether layer of the filtrate was separated, washed twice with water, and dried over anhydrous magnesium sulfate. The ether was evaporated, and the oily residue was crystallized from ethanol. The combined crude ketone was obtained as colorless platelets from ethanol, m. p. 72–75°; yield 10.0 g. (61.8%). For analysis a small portion was recrystallized twice from ethanol, m. p. 80–81°.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.56; H, 8.06.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-4-nonanone (XIb).—A solution of 10.2 g. (0.05 mole) of 1-(*p*-methoxyphenoxy)-3-cyanobutane in 40 ml. of anhydrous ether was added to a Grignard reagent prepared from 1.44 g. (0.06 mole) of magnesium, 14.8 g. (0.065 mole) of 1-(*p*-methoxyphenoxy)-5-chloropentane, and 30 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then decomposed at 0° by the slow addition of 100 ml. of 1.2 *N* hydrochloric acid. The crude ketone was isolated by filtration. The ether layer of the filtrate was separated, washed twice with water, and dried over anhydrous magnesium sulfate. The ether was evaporated, and the oil residue was crystallized from an ethyl acetate–petroleum ether mixture. The combined crude ketone was dissolved in boiling ethyl acetate and allowed to cool to 50°. One gram of non-ketonic material, m. p. 127–

(23) Robinson and Watt, *J. Chem. Soc.*, 1536 (1934).

(24) von Braun, *Ber.*, **42**, 2047 (1909).

128°, was isolated by filtration, but it was not investigated further. The 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-4-nonanone was obtained as white rosettes upon the addition of petroleum ether to the cold ethyl acetate solution, m. p. 42–43°; yield 10.2 g. (51%).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.15; H, 8.02.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-6-nonanone (XIc).—A solution of 4.76 g. (0.025 mole) of 1-cyano-3-(*p*-methoxyphenoxy)-propane in 20 ml. of anhydrous ether was added with stirring to a Grignard reagent prepared from 0.72 g. (0.03 mole) of magnesium, 9.2 g. (0.032 mole) of 1-bromo-3-methyl-5-(*p*-methoxyphenoxy)-pentane, and 20 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then decomposed at 0° by the slow addition of 50 ml. of 1.2 *N* hydrochloric acid. The ether layer was separated, washed twice with water, and dried over anhydrous magnesium sulfate. After removal of the solvent by distillation, the ketone was obtained as an oil which could not be induced to crystallize, yield 8.4 g. (84%).

Oximes

One gram (0.0025 mole) of the ketone in 15 ml. of 50% methanol was heated under reflux for eighteen hours with 0.6 g. (0.0086 mole) of hydroxylamine hydrochloride and 1.2 g. (0.0147 mole) of anhydrous sodium acetate. The oxime crystallized upon cooling and was washed with water. Recrystallization from 95% ethanol yielded 0.6 g. (60%).

1,9-bis-(*p*-Methoxyphenoxy)-4-nonanone Oxime (XIIa).—Needles, m. p. 76–77°.

Anal. Calcd. for $C_{23}H_{31}NO_6$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.93; H, 7.84; N, 3.57.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-4-nonanone Oxime (XIIb).—Platelets, m. p. 76.5–77°.

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.36; H, 8.20; N, 3.46.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-6-nonanone Oxime (XIIc).—Platelets, m. p. 78–79°.

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.65; H, 8.29; N, 3.63.

Amines

A mixture of 12.5 g. of the ketone and 50 ml. of liquid ammonia was hydrogenated over Raney nickel catalyst at 150° and 150–200 atmospheres for five hours. The amine was dissolved in ethanol, and the catalyst was separated by filtration.

4-Amino-1,9-bis-(*p*-methoxyphenoxy)-nonane (XIIIa).—The ethanol was evaporated, and the residual light yellow oil was caused to crystallize by the addition of cold ether. The pure amine was obtained in approximately 60% yield as needles upon recrystallization from anhydrous ether, m. p. 71–72°.

Anal. Calcd. for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.62. Found: C, 71.13; H, 8.48; N, 3.72.

4-Amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIb).—After removal of the ethanol by distillation, the amine was obtained as a red oil which could not be crystallized. The hydrochloride was prepared by the addition of five drops of the amine to a solution of 2 ml. of 50% ethanol and three drops of concentrated hydrochloric acid. The crude product was recrystallized from hot water as colorless platelets, m. p. 104–105°. Chemical behavior, infrared spectrum and analysis proved the compound to be 4-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane hydrochloride monohydrate (yield, *ca.* 60%).

Anal. Calcd. for $C_{24}H_{36}ClNO_4 \cdot H_2O$: C, 63.24; H, 8.40; N, 3.07. Found: C, 63.35; H, 8.63; N, 3.08.

6-Amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIc).—After removal of the ethanol by distillation, the amine was obtained as a red oil which could not be induced to crystallize. The oxalate was chosen as a derivative. A 30% ethanolic solution of anhydrous oxalic acid was added dropwise to a solution of five drops of the amine in 5 ml. of ethanol. The monoammonium monoamine oxalate was obtained as white needles, m. p. 194–196° (yield, *ca.* 40%).

Anal. Calcd. for $C_{26}H_{39}N_2O_8$: C, 61.52; H, 7.75; N, 5.52. Found: C, 61.80; H, 7.81; N, 5.87.

α,ω-Dibromoamine Hydrobromides

A solution of 9 g. of the amine (XIII) in 190 ml. of glacial acetic acid was saturated with hydrogen bromide. The solution was treated with 190 ml. of 48% hydrobromic acid and boiled under reflux for seventy-two hours. The solvents were removed by distillation under reduced pressure. The residue was dissolved in 50% ethanol and evaporated to dryness under reduced pressure. The α,ω-dibromoamine hydrobromide was not purified but was used directly in the next step.

1-Azabicyclo[5.3.0]decanes

The method of preparation of the tertiary amines (III, VII, VIII) was essentially that of Prelog, Cerkovnikov and Ustricev[25] for the synthesis of bicyclic amines possessing a bridge-head-nitrogen atom. The steam volatile tertiary base was acidified with 10% hydrochloric acid. The water was removed by distillation under reduced pressure. The residue was treated with 20 ml. of 2 *N* sodium hydroxide, extracted twice with ether, and the ethereal solution was dried over anhydrous magnesium sulfate. The ethereal solution was used for the preparation of derivatives.

1-Azabicyclo[5.3.0]decane (III) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 213–214° (reported, 213–214°,[3] 213°[2]).

8-Methyl-1-azabicyclo[5.3.0]decane (VII) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 181–182°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.46; H, 5.93; N, 14.46.

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 189°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.21; H, 5.99; N, 14.93.

8-Methyl-1-azabicyclo[5.3.0]decane (VII) Picrolonate.—Prepared in ether and recrystallized twice from ethanol, the picrolonate formed yellow needles which melted at 189–190°.

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) Picrolonate.—Prepared in ether and recrystallized twice from ethanol, the picrolonate formed deep yellow clusters of small prisms, m. p. 138–139°.

Summary

8-Methyl-1-azabicyclo[5.3.0]decane (VII) has been synthesized by an unequivocal method and has been shown to be identical with the Clemmensen reduction product of 1-keto-2-methylquinolizidine (IV).

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) has been synthesized by a similar method and has been shown to be identical with the Clemmensen reduction product of 1-keto-8-methylquinolizidine (V).

By these comparisons, it has been established that it is the ketonic ring which undergoes contraction during the Clemmensen reduction-rearrangement of 1-ketoquinolizidines.

URBANA, ILLINOIS RECEIVED FEBRUARY 21, 1949

(25) Prelog, Cerkovnikov and Ustricev, *Ann.*, **535**, 37 (1938).