Clemmensen Reduction of Mannich Bases: Potential Ganglionic and Nicotinic Agents

R. R. ISON▲ and M. M. A. HASSAN*

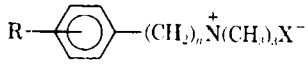
Abstract □ An attempt was made to prepare *p*-aminophenylpropyltrimethylammonium iodide (a potential ganglionic stimulant) by a route involving the Clemmensen reduction of 3-dimethylamino-1-*p*-nitrophenylpropan-1-one. The main product was the *trans*-isomer of 1-*p*-aminophenyl-3-dimethylaminoprop-1-ene, but this could be converted to the required trimethylammonium derivative by hydrogenation and methylation. The Clemmensen reduction of other Mannich bases also was investigated. 3-Dimethylamino-1-arylprop-1-enes are of particular interest because of the reported nicotinic activity of the methosalts. Several products were formed, however, including an azeotropic mixture of the aminoalkane and the aminoalkene. The azeotrope could be converted smoothly to the pure 1-aryl-3-dimethylaminopropane by catalytic hydrogenation. This route can, therefore, be used to prepare 1-arylpropyltrimethylammonium halides, which are potentially nicotine-like. Other methods for reducing the carbonyl group of Mannich bases completely are discussed.

Keyphrases □ *p*-Aminophenylpropyltrimethylammonium iodide—synthesis and screening as a potential ganglionic stimulant □ Ganglionic stimulants, potential—synthesis and screening of *p*-aminophenylpropyltrimethylammonium iodide, Clemmensen reduction of Mannich bases □ Clemmensen reduction of Mannich bases—synthesis of potential ganglionic and nicotinic agents □ Mannich bases—use of Clemmensen reduction to synthesize potential ganglionic and nicotinic agents

Some aralkyltrimethylammonium salts (I) were highly active on the isolated frog rectus abdominis muscle (1). The most active agonists were *m*-hydroxyphenethyltrimethylammonium iodide (leptodactyline iodide) (I*a*, $n = 2$), *m*-hydroxyphenylpropyltrimethylammonium bromide (I*a*, $n = 3$), and *p*-aminophenethyltrimethylammonium iodide (I*b*, $n = 3$), which were 20–50 times as potent as nicotine on this preparation. *p*-Aminophenethyltrimethylammonium iodide was found later to be the most specific as a ganglionic stimulant (2), and it was decided to prepare *p*-aminophenylpropyltrimethylammonium iodide for pharmacological evaluation. A number of arylpropenyltrimethylammonium halides (VI), which are structurally similar to the aralkyltrimethylammonium series (I), also were reported (3, 4) to possess high nicotinic activity.

DISCUSSION

A three-stage synthesis was designed (II*a* → III*b* → I*b*, $n = 3$) to prepare *p*-aminophenylpropyltrimethylammonium iodide (Scheme I). The first step involved the Clemmensen reduction (5) of 3-dimethylamino-1-*p*-nitrophenylpropan-1-one (II*a*) to the corresponding *p*-aminophenylpropylamine (III*b*). This produced the *trans*-*p*-aminophenylpropenylamine (IV*b*) in 24% yield, together with a large quantity of intractable material. The product (IV*b*) was identified by its PMR spectrum, which showed a vinylic multiplet (ABX_2, $J_{AB} = 16$ Hz.) characteristic of *trans*-1-aryl-3-tertiary-aminoprop-1-enes (6). Catalytic hydrogenation of IV*b* gave 1-*p*-aminophenyl-3-dimethylaminopropane (III*b*), from which *p*-aminophenylpropyltrimethylammonium iodide (I*b*, $n = 3$) was prepared.

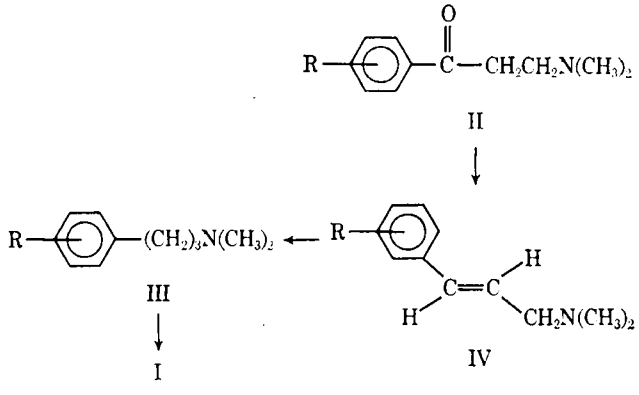


I*a*: R = *m*-OH
I*b*: R = *p*-NH$_2$

The formation of olefinic by-products in the Clemmensen reaction is well established (7), but there appears to be no report relating to the reduction of β-aminoketones (II). The isolation of *trans*-1-*p*-aminophenyl-3-dimethylaminoprop-1-ene (IV*b*) from the reaction, however, was of much interest, because the quaternary methiodide derivatives (VI) of such aminoalkenes have been reported (3, 4) to be highly active nicotinic agents. It was, therefore, decided to see whether aminoalkenes were consistently formed with other Mannich bases (Table I), three of which (II*c*, II*d*, and II*e*) were studied in detail. The Clemmensen reduction gave two products in low yield[1]: (*a*) an azeotropic mixture of the appropriate aminoalkane[2] (III) and aminoalkene[2] (IV), and (*b*) a high boiling liquid which could be crystallized. The solid product appeared to be a mixture of the *meso*- and *dl*-forms of the dimer[3] (V) and was probably formed by the addition of two electrons and protons from the Clemmensen reagent (8) to the Mannich base.

With the three other β-aminoketones (II*f*, II*g*, and II*h*), no attempt was made to isolate the corresponding dimers. Only the low boiling distillate was collected, and it was again found to be a mixture of aminoalkane and aminoalkene[2]. The formation of pure aminoalkene (IV*b*) in the initial reaction seems to depend on the presence of the nitro group, which may prevent complete reduction. The exact mechanism of the Clemmensen reduction of β-aminoketones is obscure, but the formation of aminoalkenes may involve a monomeric alcohol[4] intermediate (7).

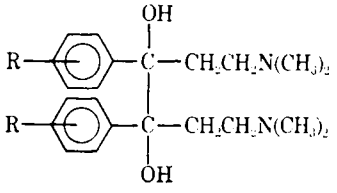
The carbonyl group in Mannich bases appears to be very difficult to reduce to methylene; treatment of both the phenyl and *o*-tolyl aminoketones with the lithium aluminum hydride–aluminum



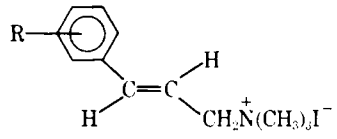
II–IV *a*: R = *p*-NO$_2$
b: R = *p*-NH$_2$
c: R = H
d: R = *p*-F
e: R = *p*-Cl
f: R = *m*-CF$_3$
g: R = *o*-CH$_3$
h: R = *p*-CH$_3$

Scheme I

[1] A large amount of intractable resinous material was evident after distillation of each crude Clemmensen product.
[2] Proton magnetic resonance evidence.
[3] Mass spectral total ion-current evidence.
[4] When one reaction with II*c* was terminated by basification after 3 hr., a sample of 3-dimethylamino-1-phenylpropan-1-ol hydrochloride (3%) was isolated, m.p. 135°, identical to authentic material (6), but the ratio of the other products remained unchanged.



V



VI

chloride reagent, which has been suggested as an alternative to the Clemmensen reduction (15), gave only the corresponding secondary alcohols. Both the carbonyl and the *p*-nitro groups of the Mannich base (II*a*) could be reduced, however, when the compound was suspended in ethanolic hydrogen chloride and hydrogenated at room temperature and atmospheric pressure for 14 days with palladium-on-carbon as catalyst[5]. This method provided another route to *p*-aminophenylpropyltrimethylammonium iodide (I*b*, n = 3).

PHARMACOLOGY

p-Aminophenylpropyltrimethylammonium iodide showed no hypotensive effects in the pithed rat and acted as a weak blocker[6]. It was only one-tenth as active as *p*-aminophenethyltrimethylammonium iodide (I*b*, n = 2) when tested for ganglionic stimulant activity on the isolated guinea pig ileum.

EXPERIMENTAL[7]

β-Aminoketone Hydrochlorides (II)—The hydrochloride salts of II*a*–II*h* were prepared by the usual method (16) from the appropriately substituted acetophenones. The melting points of II*a* (17), II*c* (9), II*d* (10), II*e* (11), II*f* (12), II*g* (13), and II*h* (14) were in agreement with literature values.

***trans*-1-*p*-Aminophenyl-3-dimethylaminoprop-1-ene (IV*b*)**—A solution of mercuric chloride (5 g.) in 10% HCl (100 ml.) was shaken (5 min.) with granulated zinc (60 g.) as previously described (5), and the amalgam was rinsed with water. 3-Dimethylamino-1-*p*-nitrophenylpropan-1-one hydrochloride (17) (II*a*) (38 g., 0.147 mole) was dissolved in 35% HCl (150 ml.), and the solution was added dropwise to the amalgam. The vigorous reaction was kept under control by cooling under the tap before a further portion of 35% HCl (100 ml.) was added and the mixture was refluxed overnight. The solution was basified with enough ammonium hydroxide to redissolve the zinc hydroxide precipitate and was then extracted with ether and dried (sodium sulfate). Evaporation of the extracts gave an oil (14 g.) which, when distilled *via* a Vigreux head, gave 5.4 g. (24%) of the product, b.p. 121° (0.35 mm.), n_D^{25} = 1.5960. The proton magnetic resonance (PMR) spectrum ($CDCl_3$) agreed well with that of the parent alkene (IV*c*) (6). The product formed an unstable *methiodide*, which formed a light-sensitive *hydrogen iodide*, m.p. 215–217° (methanol–ether), λ_{max} 282 nm. (ε 21,900).

Anal.—Calc. for $C_{12}H_{22}I_2N_2$: C, 32.04; H, 4.69; N, 6.28. Found: C, 32.30; H, 4.51; N, 6.28.

***p*-Aminophenylpropyltrimethylammonium Iodide (I*b*, n = 3)**—The aminoalkene (IV*b*) (1 g.) was dissolved in a mixture of ethanol and 10% palladium-on-carbon (0.4 g.) and hydrogenated overnight at room temperature and atmospheric pressure. The reaction mixture was filtered (kieselguhr), and the filtrate was evaporated to a small volume. After the addition of methyl iodide (2 ml.) and a few drops of ether, the product separated as gold needles (1.2 g.), m.p. 204–205°; PMR (D_2O): vinylic signals absent.

Anal.—Calc. for $C_{12}H_{21}IN_2$: C, 45.01; H, 6.61. Found: C, 44.79; H, 6.83.

Other Clemmensen Reductions—These were carried out in the manner described for IV*b*. Distillation of the crude products derived from II*c*, II*d*, and II*e* gave two fractions (Table I) with the following characteristics:

A mixture of III*c* and IV*c*, b.p. 62° (0.20 mm.), and the isomeric *dimer* V*c*, b.p. 168° (0.25 mm.), m.p. 148–150° (ethanol); M^+ at *m/e* 356 ($C_{22}H_{32}N_2O_2$) (both isomers).

Anal.—Calc. for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05. Found: C, 74.22; H, 8.89.

A mixture of III*d* and IV*d*, b.p. 66–68° (0.20 mm.), and the isomeric *dimer* V*d*, b.p. 168–169° (0.30 mm.), m.p. 170–172° (ethanol); M^+ at *m/e* 392 ($C_{22}H_{30}F_2N_2O_2$) (both isomers).

Anal.—Calc. for $C_{22}H_{30}F_2N_2O_2$: C, 67.32; H, 7.70. Found: C, 67.58; H, 7.48.

A mixture of III*e* and IV*e*, b.p. 80–82° (0.10 mm.), and the isomeric *dimer* V*e*, b.p. 230° (0.20 mm.), m.p. 198–200° (ethanol); M^+ at *m/e* 425/427 ($C_{22}H_{30}Cl_2N_2O_2$) (both isomers).

Anal.—Calc. for $C_{22}H_{30}Cl_2N_2O_2$: C, 62.11; H, 7.11. Found: C, 62.22; H, 7.09.

The aminoalkene–aminoalkane mixtures from the *m*-CF_3, *o*-CH_3, and *p*-CH_3 Mannich bases (II*f*, II*g*, and II*h*, respectively) were collected at ~70° (0.20 mm.) in various ratios (Table I).

In all the reductions specified, the PMR spectra ($CDCl_3$ and tetramethylsilane) of the low boiling products were compatible with mixtures of the aminoalkene (IV) and the aminoalkane (III). In most cases, direct comparison was possible with the PMR spectra of authentic aminoalkenes and aminoalkanes prepared by standard methods. The aminoalkanes showed $N(CH_3)_2$ singlets at higher field (~0.08 p.p.m.) than the corresponding signals for the aminoalkenes. The integral ratios of the $N(CH_3)_2$ peaks were used to assess the product ratios (Table I).

Lithium Aluminum Hydride–Aluminum Chloride Reductions—Treatment of 3-dimethylamino-1-phenylpropan-1-one (II*c*) with ethereal lithium aluminum hydride–aluminum chloride in the usual manner (15) gave 3-dimethylamino-1-phenylpropan-1-ol, identical to authentic material (6).

Similarly, lithium aluminum hydride–aluminum chloride reduction of 3-dimethylamino-1-*o*-tolylpropan-1-one (13) gave 3-dimethylamino-1-*o*-tolylpropan-1-ol, which formed a *methiodide*, m.p. 152–154° (ethanol–ether).

Anal.—Calc. for $C_{13}H_{22}INO$: I, 37.86. Found: I, 37.88.

Catalytic Reduction of 3-Dimethylamino-1-*p*-nitrophenylpropan-1-one (II*a*)—II*a* hydrochloride (17) (7.7 g.) was suspended in ethanol (100 ml.), and the mixture was saturated with hydrogen chloride gas. Most substrate went into solution and, after cooling, 10% palladium-on-carbon (0.5 g.) was added and the reaction mixture was hydrogenated at room temperature and atmospheric pressure until hydrogen absorption ceased (14 days). The filtered solution (kieselguhr) was evaporated to dryness, the residual solid was treated with ammonium hydroxide, and the liberated base was extracted into ether and dried (magnesium sulfate). Evaporation of the extracts gave an oil (5 g.), which was distilled to give 1-*p*-aminophenyl-3-dimethylaminopropane (III*b*), b.p. 120° (0.1 mm.), n_D^{20} = 1.5430, which formed the *methiodide* (I*b*, n = 3), m.p. 203–

Table I—Reaction Products from Clemmensen Reduction of Mannich Bases

R-$C_6H_4COCH_2CH_2N(CH_3)_2$ (II)	Aminoalkene (IV)–Aminoalkane (III), % Yield[a]	Dimer (V)
II*c*, R = H (9)[b]	13 (1:1)	28
II*d*, R = *p*-F (10)	17[c]	18
II*e*, R = *p*-Cl (11)	29 (1:1)	9
II*f*, R = *m*-CF_3 (12)	27 (1:1)	—
II*g*, R = *o*-CH_3 (13)	27 (3:2)	—
II*h*, R = *p*-CH_3 (14)	26 (1:2)	—

[a] Product ratio from proton magnetic resonance integral data in parentheses. [b] Reference. [c] Greater than 90% aminoalkene.

[5] The authors thank Dr. J. M. Osbond, Roche Products Limited, Welwyn Garden City, Herts., U.K., for suggesting these reaction conditions.

[6] D. S. McQueen, Department of Pharmacology, University of Edinburgh, Edinburgh EH89JZ, U. K., personal communication.

[7] Melting points were recorded on a Mettler FP1 instrument connected to a pen recorder. The NMR spectra were recorded on Perkin-Elmer R10 and Varian HA-100 instruments. Mass spectrometry was carried out with an LKB-9000 (ev. 27.5).

204°, identical (PMR, mixed melting point) to the material prepared previously by the Clemmensen route.

CONCLUSIONS

Clemmensen reduction of Mannich bases leads to a variety of products, but the reaction can still be used to prepare members of the arylpropylamine series. Catalytic hydrogenation of the low boiling fraction distilled from the crude product ensures complete saturation of the side chain and the isolation of pure aminoalkane (III). These derivatives can then be converted to phenylpropyltrimethylammonium derivatives (I, n = 3), which have potential nicotinic properties (1).

REFERENCES

(1) R. B. Barlow, G. M. Thompson, and N. C. Scott, *Brit. J. Pharmacol.*, **37**, 555(1969).

(2) R. B. Barlow and F. Franks, *ibid.*, **42**, 137(1971).

(3) K. C. Wong and J. P. Long, *J. Pharmacol. Exp. Ther.*, **137**, 70(1962).

(4) P. L. Kirkendol, R. A. Woodbury, and E. E. Elko, *Arch. Int. Pharmacodyn. Ther.*, **196**, 25(1972).

(5) E. L. Martin, *Org. React.*, **1**, 155(1942).

(6) R. R. Ison and A. F. Casy, *J. Chem. Soc. B*, **1971**, 230.

(7) R. L. Augustine, "Reduction—Techniques and Applications in Organic Synthesis," Arnold, London, England, 1968, pp. 186–194.

(8) B. R. Davis and P. D. Woodgate, *J. Chem. Soc. C*, **1966**, 2006.

(9) C. E. Maxwell, *Org. Synth.*, **23**, 20(1943).

(10) A. F. Casy and P. Pocha, *J. Chem. Soc. B*, **1966**, 1160.

(11) D. W. Adamson and J. W. Billinghurst, *J. Chem. Soc.*, **1950**, 1039.

(12) B. Brunova, V. Musil, Z. Horakova, and O. Nemecek, *Cesk. Farm.*, **18**, 28(1969); through *Chem. Abstr.*, **71**, 112852b (1969).

(13) J. H. Burckhalter and S. H. Johnson, *J. Amer. Chem. Soc.*, **73**, 4827(1951).

(14) D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones, *J. Chem. Soc.*, **1958**, 312.

(15) R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896(1958).

(16) F. F. Blicke, *Org. React.*, **1**, 303(1942).

(17) H. F. Ginsberg, I. Lederman, and D. Papa, *J. Amer. Chem. Soc.*, **75**, 4587(1953).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 14, 1972, from the *Department of Pharmacology, University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, United Kingdom.*

Accepted for publication March 12, 1973.

The authors thank Mrs. M. Groves and Mr. J. Millar for recording the NMR spectra and Dr. C. J. Thompson for determining the mass spectra. R. R. Ison acknowledges a Roche fellowship and support from the Corfield Memorial Trust.

* On study leave from the Faculty of Pharmacy, University of Riyadh, Saudi Arabia.

▲ To whom inquiries should be directed.

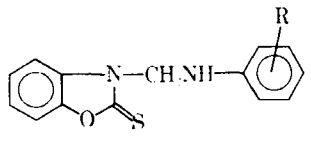
Potential Biologically Active Agents V: Synthesis and Pharmacological Screening of Substituted 3-Aminomethylbenzoxazolin-2-thiones

RAJENDRA S. VARMA

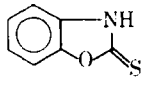
Abstract □ A series of substituted 3-aminomethylbenzoxazolin-2-thiones was synthesized and evaluated for antibacterial activity.

Keyphrases □ 3-Aminomethylbenzoxazolin-2-thiones—synthesized and screened as potential antibacterial agents □ Antibacterial agents, potential—synthesis and screening of 3-aminomethylbenzoxazolin-2-thiones □ Benzoxazolin-2-thiones, substituted—synthesized and screened as potential antibacterial agents

Benzazoles have been reported to exhibit diverse biological properties. The 2- and 3-substituted benzoxazolinone analogs have shown anticonvulsant (1) and antimicrobial (2, 3) activities. Antitubercular (4), antispasmodic (5), and antibacterial (6–9) activities have been observed for benzothiazolin-2-thione and 2-alkylmercaptobenzothiazoles. Substituted 3-aminomethylbenzothiazolin-2-thiones have displayed antimicrobial (10, 11) activity. Further antimicrobial (12, 13), diuretic (14), cancerostatic (15), antitubercular (15), hypoglycemic (16), parasympatholytic (17), and herbicidal (18) properties have been associated with benzoxazolin-2-thiones. In view of these reports, it was of interest to synthesize substituted 3-aminomethylbenzoxazolin-2-thiones (I) for biological screening. The synthesis of I was achieved by condensing benzoxazolin-2-thione (II), formaldehyde, and an amine.



I



II

BIOLOGICAL DATA

The compounds listed in Table I were screened for their inhibitory effect against *Escherichia coli* and *Staphylococcus aureus*[1] by the agar diffusion technique (19). Four compounds (I, VII, XII, and

[1] Bacterial cultures maintained at Central Drug Research Institute, Lucknow, India, were used.