Annals of Chemistry: Open Access
Received: Nov 06, 2015, Accepted: Dec 14, 2015, Published: Dec 17, 2015
Arts Lit Linguist, Volume 1, Issue 1
http://crescopublications.org/acoa/ACOA-1-002.pdf
Article Number: ACOA-1-002

Research Article Open Access

Synthesis and S-Alkylation of some Novel Nitro-Mannich Bases

Mardia T El Sayed[1*], El Sayed M Afsah[2] and Dalia A Osman[3]

[1]Applied Organic Chemistry Department, National Research Centre, Cairo, Dokki, Egypt
[2]Chemistry Department, Faculty of Science, El-Mansoura University, Mansoura, Egypt
[3]Photo Chemistry Department, National Research Centre, Cairo, Dokki, Egypt

***Corresponding Author:** Mardia T El Sayed, Applied Organic Chemistry Department, National Research Centre, Cairo, Dokki, Egypt, E-mail: mardia_elsayed2009@aol.com

Citation: Mardia T El Sayed, El Sayed M Afsah and Dalia A Osman (2015) Synthesis and S-Alkylation of some Novel Nitro-Mannich Bases. Ann Chem Open Access 1: 002.

Abstract

Mannich reactions using nitroalkanes and related compounds as substrates are of synthetic relevance and the products are promising as biologically active substances. A number of nitro-heterocycles of pharmacological interest were also synthesized by Mannich reactions with suitable nitro-substrates. In view of this, and because of the widespread and increasing interest in the chemistry of Mannich bases, the present work focused on exploring the reactivity of nitromethane towards Mannich reaction with heterocyclic amines, diamines and hydrazine derivatives. The synthetic potential of the nitro-Mannich bases for the synthesis of a variety of N- and S- nitroheterocycles of pharmaceutical interest has been investigated.

Keywords: Nitroalkanes, Mannich reaction

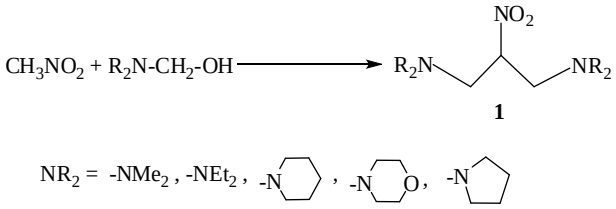
Body of the Article

The chemistry of Mannich bases has been the subject of wide and increasing interest. Mannich bases are potentially versatile synthetic intermediates, and are used for the synthesis of a variety of carbocyclic, heterocyclic compounds and natural products. There is also increasing interest in Mannich bases due to their wide range of biological and pharmacological activities [1-7]. Mannich reaction (Aminomethylation) consists of the condensation of ammonia, primary or secondary amine, usually as the hydrochloride, with formaldehyde (or, occasionally other aldehydes) and a substrate (any heterocyclic ketone possessing at least one active hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an amino methyl or substituted amino methyl group.

The Mannich reaction using nitroalkanes and related compounds as substrates is of synthetic relevance, and the products are promising as biologically active substances. Successful synthesis of nitro Mannich bases derived from nitroalkanes and morpholine or piperidine has been reported [8-10]. It is known that the nitro group is an important constituent of many biologically significant heterocycles, such as the antibiotic drugs nitrofurantoin [11] & nitrofurazone [11].

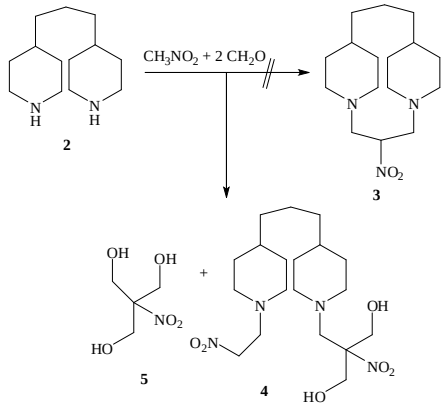
Mannich Reaction with Secondary Amines

In view of this and the present work is concerned with attempts to extened the scope of Mannich reaction with nitroalkanes to include the synthesis of a variety of nitro N- and Sheterocycles. It has been reported [9,12,13] that Mannich reaction with nitromethane and nitroethane tend to yield nitro bis-bases of the type 1, which are useful starting materials for the synthesis of 1,2,3-triaminopropanes by reduction, (Scheme 1).



Scheme 1

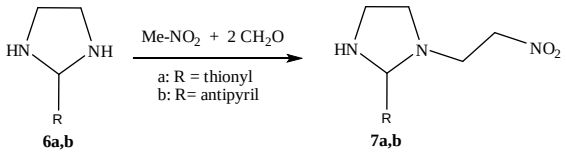
In order to determine the generality and to extend the scope of this double Mannich reaction, the author investigated the reactivity of several heterocyclic amines, diamines and hydrazines with nitromethane under the Mannich reaction conditions. Therefore, successive treatment of nitromethane with formaldehyde and Nphenylpiperazine yielded 1, 3-di [N (N`-phenylpiperazino)]-2-nitropropane (1). The formation of 1 takes place *via* a double Mannich reaction is in line with the previously reported [14, 15]. In view of this, the author investigated the Mannich reaction of nitromethane with 4, 4`-trimethylenedipiperidine (2) and formaldehyde, as a possible route to the macroheterocyclic system (3). However, such reaction afforded 4 as the major product with small amount of tris (hydroxymethyl) nitromethane (5), and none of the cyclized product 3 was obtained. The major product was identified as *N*-[2, 2-di (hydroxymethyl)-2-nitroethyl]-*N*`-(2-nitroethyl)-4, 4`-trimethylenedipiperidine dihydrate (4), (Scheme 2).



Scheme 2

The analytical, IR and mass spectral data of 4 are consistent with the molecular formula C19H36N4O6. 2H2O. the IR spectrum showed a strong broad band at 3447 (OH hydrate), 1556 and 1345 (NO2). Its mass spectrum exhibits a molecular ion peak at m/z 452 (M+) and 453 (M++1). The base peak at m/z 141 (100 %) is due to the N-(3-hydroxypropyl) tetrahydropyridine ion. The fragmentation pattern of 4 is depicted in the scheme (3). The ions at m/z 170, 169, 152, 139 and 141 are consistent with the presence of an *N*-[2, 2-di (hydroxymethyl)-2-nitro-ethyl] piperidine unit. Obviously, the trimethylol derivative (5) is an intermediate in the reaction sequence, and its formation, from nitromethane and formaldehyde, is expected and this compound has been previously reported [16]. Evidence in favour of this mechanism is that the trimethylol derivative (5) has been isolated. In line with this, Mannich reaction of nitromethane with 2-(2-thienyl) imidazolidine (6a, b) (compound 6a, b was prepared from ethylenediamine and 2-thiophene aldehyde or 4-antipyrine aldeyde) (c.f. experimental section) and formaldehyde led to the formation of *N*-(2-nitroethyl)-2-(2-thienyl) imidazolidine (7a, b), (precipitated from the reaction mixture), as a result of participation of one amino group in the reaction. This behaviour has been attributed to steric and solubility factors.

In its IR spectrum compound 7a, b showed bands characteristic of (NH) 3435 and (NO2) 1536 and 1336cm-1. The mass spectrum exhibits a molecular ion peak at m/z 227 (M+), it underwent fragmentation pattern which supported its structure (Scheme 3).

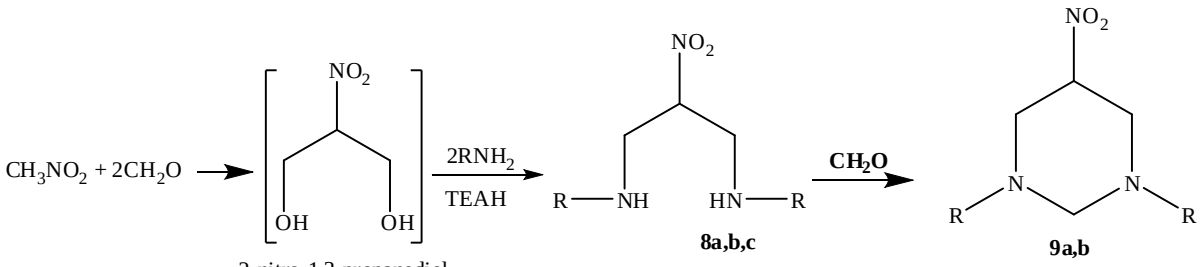


Scheme 3

Mannich Reaction with Primary Amines

Very few cases were reported in the literature [15, 17] for the use of primary amines in Mannich reaction with nitroalkanes. In the present work, the author prepared N,N`-diaryl-2-nitro-1,3-propanediamines (8a, b) by treating nitromethane with formaldehyde, the 2-nitro-1,3-propanediol was formed in situ, and this reacted with p-toluidine or p-hydroxyaniline or 4-aminoantipyrine in presence of tetraethylammonium hydroxide (TEAH) to give 8a,b, respectively.

The nitro bis-bases (8a, c) possessing 1, 5-secondry diamino groups are useful synthones for the synthesis of hexahydro-nitropyrimidines [18]. Therefore, the successful synthesis of 1,2,3,4,5,6-hexahydro-1, 3-di (p-tolyl)-5-methyl-5-nitropyrimidine (9a, b) was accomplished by treating 8a, b with formaldehyde. The 1H NMR of 9a showed characteristic signals at δ 3.3 (4-Ha and 6-Ha), and 4.20 (4-Hb and 6-Hb), and 4.30, 4.60 (N-CH2-N), and lacked signals due to NH protons. 9b was determined as 1,2,3,4,5,6-hexahydro-1, 3-di (4-antipyrinyl)-5-nitropyrimidine (Scheme 4).



2-nitro-1,3-propanediol

8a,b,c

R = a: 4-Me-Ph, b: 4-OH-Ph, c: antipryil

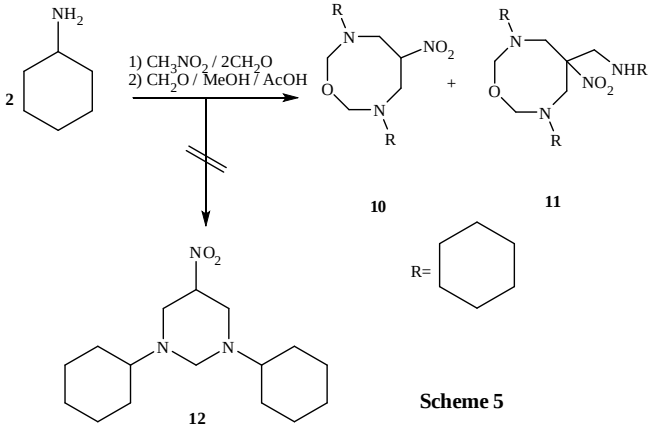
9a,b

R = a: 4-Me-Ph, b: antipryil

Scheme 4

The structural features of compounds 8c and 9b which have two antipyrine units are of interest. However, this synthetic route to hexahydro-nitro-pyrimidines is of particular practical interest, since the resultant pyrimidines, such as 9a, b with nitro functionality at C-5 and two aromatic or heterocyclic moieties at *N*-1 and *N*-3 are not easily avaible by other methods. The analytical, IR and MS spectral data are consistent with the structures proposed for compounds 24-29 (cf. experimental section). The IR spectrum of 8a, as example, showed strong absorption bands at 3407 (NH), 1294 (C-N stret. of sec. aromatic amine), 1543 and 1342 cm-1 (NO2). Cyclization of 8a to 9a and 8c to 9b was demonstrated by the absence of the band due to the (NH) group in the IR spectra of the nitro pyrimidines 9a, b. The formation of 26 and 29 is in line with some reported cases [18, 19] in which hexahydropyrimidines are obtained from 1, 5-diamines and aldehydes.

It is of interest in this connection that treatment of nitromethane with cyclohexylamine and excess formaldehyde in ethanol-acetic acid yielded a mixture of two products, which were separated by preparative TLC. The higher melting one (mp. 102º) was identified as: 3,4,5,6,7,8-hexahydro-3,7-dicyclohexyl-5-nitro-2H-1,3,7-oxadiazocine (10). The other product (11) (mp. 65º), was found to be the 5-cyclohexylaminomethyl derivative of 10. Whereas, the expected compound 12 was not obtained.

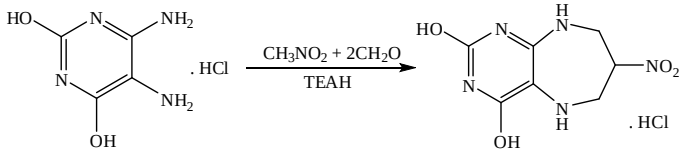


Scheme 5

Formulation of structures 10 and 11 was based on analytical and spectral data. The IR spectrum of 30 showed bands characteristic of (NO2) 1534 and 1350, and (CH2-O-CH2) 1087cm-1, whereas, compound 11 showed bands at 1546 and 1355 (NO2), 1085 (CH2-O-CH2, asym. stretch) and 3445cm-1 (NH). The mass spectra of compounds 10 and 11 showed the molecular ions at m/z 325 (M+) and 435 (M+-1), respectively, it underwent fragmentation pattern which supported their structures, (cf. scheme 12 and 13). The base peak of 10 m/z 261 (100 %) is due to [M+-(NO2+H2+O)], whereas that of 11 is m/z 55 (100 %) which corresponds to the radical cation of the azine (CH2=N-N=CH)+, (cf: schemes 12 and 13). An interesting point about the mass spectral data is that the mass spectra of 10 and 11 revealed striking similarity. Both exhibited a number of identical peaks, particularly, at m/z 324, 279, 278 and 261, which are consistent with the presence of a 1,3,7-oxadiazocine ring, as the main nucleus in the two compounds. The 5-cyclohexylaminomethyl side chain of 11 can be identified by the peak at m/z 112 (12.1%) [C6H11.NH.CH2]. The reactions described in Scheme 5 constitute a useful synthetic approach to the functionalized hexahydro-2H-1,3,7-oxadiazocines.

Mannich Reaction with Diamines

The cyclocondensation of the ketonic Mannich bases, 3-dialkylaminopropiophenone hydrochlorides with o-phenylenediamine has been reported recently [20] as a route to -2,3-dihydro-1,5-benzodiazepines. Several 1,4 and 1,5-benzodiazepines have been synthesized because of their potent activity as psychotherapeutic agents [20,21]. In the present work, the synthesis of the 7H-pyrimido[4,5-b][1,4]diazepine ring system has been achieved, by treating 5,6-diamino-2,4-dihydroxypyrimidine hydrochloride (13) with nitromethane and formaldehyde, in presence of tetraethylammonium hydroxide (TEAH), as basic catalyst, to give 5,6,8,9-tetrahydro-2,4-dihydroxy-7-nitro-pyrimido[4,5-b][1,4]diazepine hydrochloride (14), (Scheme 6), in a good yield.

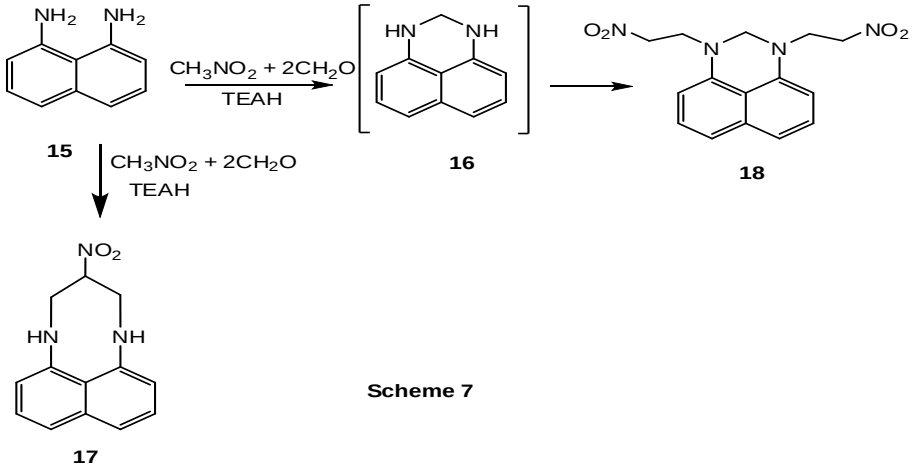


13

Scheme 6

14

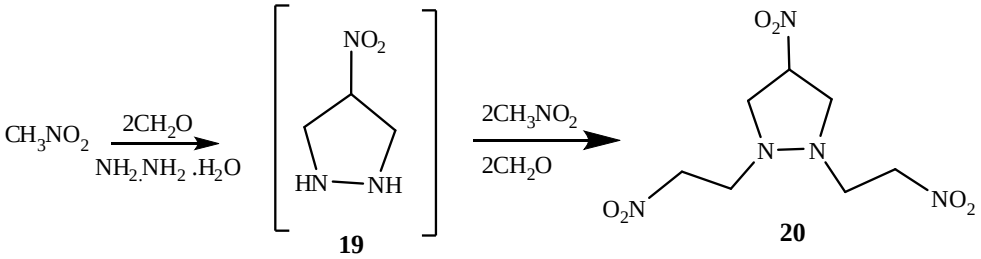
In the course of this study, the author investigated the reaction of 1,8-diaminonaphthalene **(15)** with nitromethane and formaldehyde, in presence of TEAH, anticipating the formation of the naphtha [1,8-bc][1,5]diazocine ring system (17). However, this reaction was found to take a different course, leading to 2,3-dihydro-1,3-di (2-nitroethyl) perimidine (18). It is believed that the action of formaldehyde on 15 leads initially to cyclization to 2,3-dihydroperimidine (16), which undergo double Mannich reaction with nitromethane to give 18 as a sole product, (Scheme7).



Scheme 7

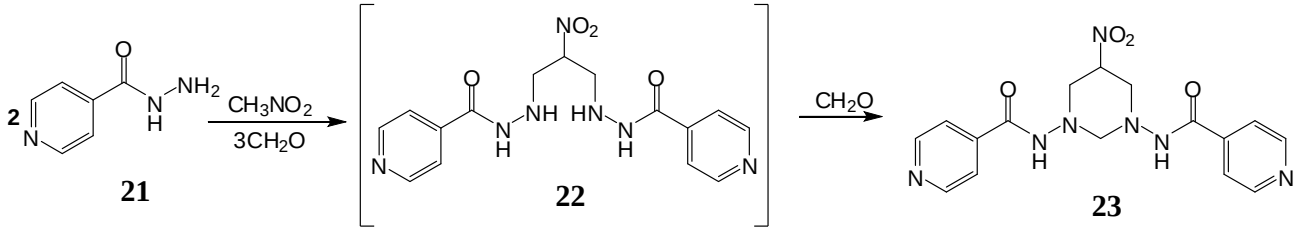
Mannich Reaction with Hydrazines

Although a wide variety of amines have been used in the Mannich reaction, the use of hydrazines in such reaction has been reported in a limited number of cases [22]. In the present study, the synthetic possibilities afforded by replacing amines by hydrazines in the Mannich reaction with nitromethane have been investigated. However, it was found that the reaction product depends on the nature of the N-substituent of the hydrazine used. Therefore treatment of hydrazine hydrate with nitromethane and formaldehyde in a molar ratio (1:1:2), afforded a single product, which was identified as: 1,2-di (2-nitroethyl)-4-nitro-pyrazolidine hydrate (20), instead of the expected 4-nitropyrazolidine (19) (Scheme 8).



Scheme 8

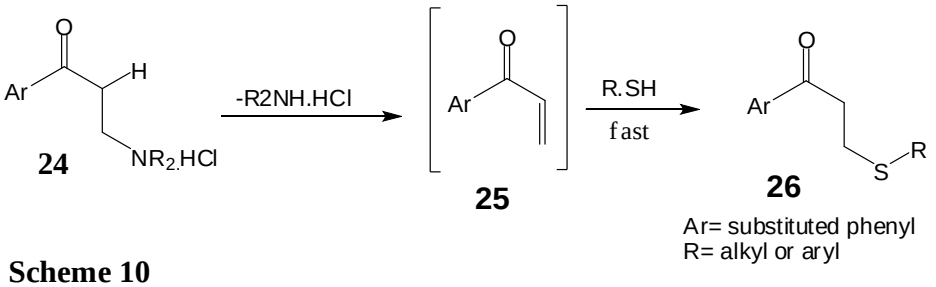
In connection with the present study, the reactivity of isonicotinic hydrazide (21), towards Mannich reaction with nitromethane and formaldehyde was investigated. Such reaction in a molar ratio (2:1:3) proceeds with cyclization to give 1,2,3,4,5,6-hexahydro-1,3-di (isonicotinoylamino)-5-nitropyrimidine (23). The formation of 23 parallels the formation of compounds 9a, b from p-toluidine and 4-aminoantipyrine respectively (Scheme 4). Accordingly, it is believed that the Mannich reaction with 21 involves the intermediacy of 22, which undergo cyclization with formaldehyde to give 23. The structure of 23 is supported by analytical and spectral data, (Scheme 9).



Scheme 9

S-Alkylation of some Nitro bis-Mannich Bases

The synthetic potential of Mannich bases as alkylating agents for active methylene compounds, thiols and amines, formed the subject of extensive investigation by numerous workers [1, 2, 3, 23, 24, 25]. The S-alkylation of thiols with ketonic Mannich bases 24 has been investigated due to its pharmacological relevance [1, 3]. The mechanism of this reaction, consists of deamination of the Mannich base to give vinyl ketone (25), followed by fast addition of the thiol yielding the α-keto sulphide (26) (Scheme 10).

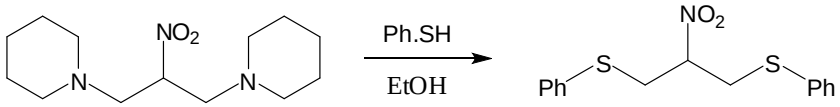


24 **25** **26**

Ar= substituted phenyl
R= alkyl or aryl

Scheme 10

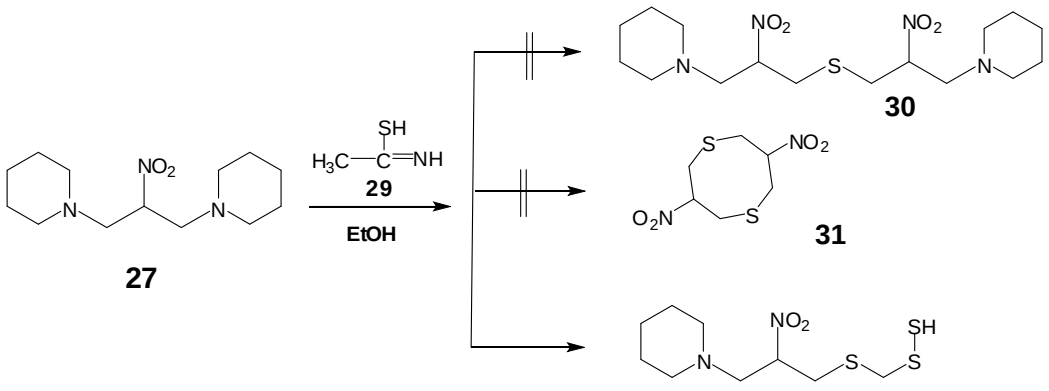
This reaction has been carried out using Mannich bases derived from ketones, phenols and indoles [26, 19, 27-29]. Whereas, there is no reported cases in the literature for using Mannich bases derived from nitroalkanes in such reaction. In the present study, the author investigated the S-alkylation of thiols with the nitro bis-base (27), and some interesting results were obtained in this direction. Thus, 1,3-di (*N*piperidino)-2-nitropropane (27) was prepared according to an earlier report [14]. Treatment of 27 with thiophenol afforded a good yield of the expected 1,3-di (phenylthio)-2-nitropropane (28). The IR spectrum of 28 showed strong absorption bands at 1545 and 1375 (NO2, asym and sym. stret) and two strong bands at 751 and 695cm-1 (mono substituted benzene ring) (Scheme 11).



27 **28**

Scheme 11

In view of the reported [29] formation of bis-(β-acylethyl) sulphides [(Ar. Co. CH2CH2)2-S], by treating ketonic Mannich bases of the type 27 with thioacetamide 29. It was expected that either the dinitro-sulphide derivative 30 or 3,7-dinitro-1,5-dithiacyclooctane (31), might be obtained by a similar reaction with 27. However treatment of 27 with thioacetamide afforded a product which was identified on the bases of its analytical and sepectral data as: 6-nitro-7-(*N*-piperidino)-1,2,4- trithiaheptane (32) (Scheme 12).

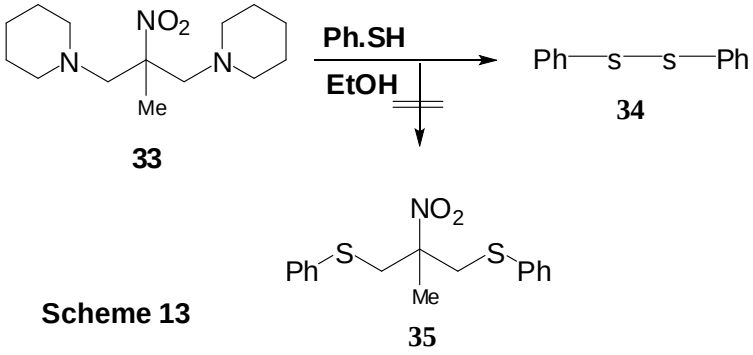


27 **30** **31** **32**

Scheme 12

The analytical and mass spectral data of 32 were consistent with the molecular formula C9H18N2O2S3. Its IR spectrum showed a strong broad band centered at 3429 (-SH) and two strong bands at 1546 and 1361cm-1 (NO2). The mass spectrum of 32 underwent fragmentation pattern which supported its structure (cf: scheme 32). The base peak at m/z 84 (100%) is due to the (*N*-piperidino) fragment. The fragments at m/z 125, 111, 79, 65 and are consistent with the presence of the (-CH2-S-CH2-S-SH) moiety. A very intense ion at m/z 56(77.5%) is found in the spectrum. This is probably due to fragmentation of the *N*-piperidinomethyl ion m/z 98(83.4%). The 1HNMR of 32 showed characteristic signals at δ 1.69-1.72 (m, 6H, 3CH2 of piperidine ring), 2.17 (m, 4H, 2CH2 of piperidine ring), 2.80-3.15 (m, 4H, (C-CH2-N), (C-CH2-S), 3.50 (s, 2H (S-CH2-S). 4.00 (m, 1H, CH.NO2).

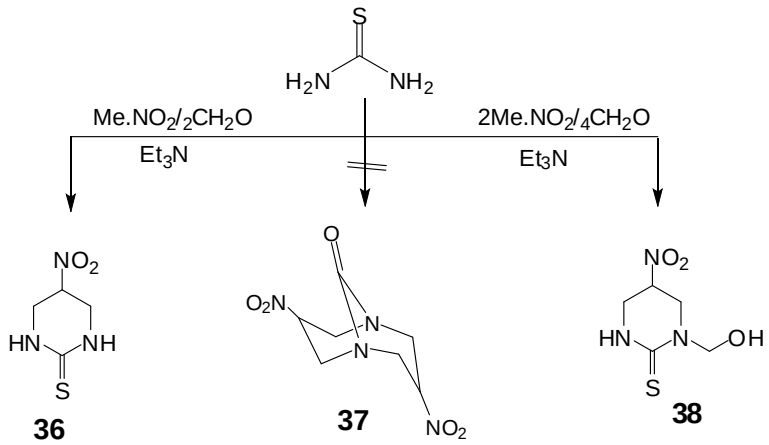
In an extension of the present study, it was found that treatment of 2-methyl-2-nitro-1,3-bis-(*N*-piperidino)propane (33) [11], with thiophenol lead to the formation of diphenyl disulphide (34), rather than the expected compound (35), in a poor yield. The mass spectrum of 34 showed the molecular ion at m/z 218(7.9%) (M+), the base peak m/z 65(100%) (S-S+H) and the M+/2 ion at m/z 109 (64%) (Ph-S) (Scheme 13).



33 **34** **35**

Scheme 13

In the course of this study, the author synthesized 1,2,3,4,5,6-hexahydro-5-nitro-2-thioxopyrimidine (36), by treating thiourea with nitromethane and formaldehyde in presence of triethylamine. Attempts have also been made to prepare the hetero bi-cyclic ring system (37), by using the same reactants in a molar ratio 1:2:4, but the only product obtained was the N-hydroxymethyl derivative (38), (Scheme 14). The structure of compounds 36 and 37 was supported by analytical and spectral data.



36 **37** **38**

Scheme 14

Acknowledgment

The authors would like to acknowledge Applied Organic Chemistry department, National Research Centre, Giza, Egypt, and the Department of Chemistry, Faculty of Science, Mansoura University

References

[1] Tramontini M, Synthesis, 703 (1973).
[2] Tramontini M, ibid, 605 (1982).
[3] Tramontini M and Angiolini L, Tetrahedron, 46, 1791 (1990).
[4] Arend M, Westerman B and Risch N, Angew. Chem., Int. Ed. Engl., 37, 1045 (1998).
[5] Ha, H-J. and Lee, W.K., Heterocycles, 57, 1525 (2002).
[6] Gul, H., Qjanen, T. and Hanninen, O., Biol. Pharm. Bull., 25, 1307 (2002).
[7] Lorand, T., et al., Eur. J. Med. Chem., 37, 803 (2002).
[8] Belikov, V.M., et. al., Tetrahedron, 26, 1199 (1970).
[9] Zief, M. and Mason, J.P., J. Org. Chem., 8, 1 (1943).
[10] Johnson, H.G., J. Amer. Chem. Soc., 68, 12 (1946).
[11] The Merk Index of Chemicals and Drugs, 9th ed., items No. 6421 and 6422.
[12] Hahn, W.E. and Zawadzka, H., Roczniki Chem., 38, 557 (1964); [C.A., 61, 106685d (1964)].
[13] Novikov, S.S. et al., Ser. Khim., 1833-9 (1967); [C.A., 68, 29687-9 (1968)].
[14] Blomquist, A.T. and Shelley, T.H., J. Amer. Chem. Soc., 70, 147 (1948).
[15] Johnson, H.G., ibid., 68, 14 (1946).
[16] The Merk Index of Chemicals and Drugs, 9th ed., item No. 9419.
[17] Senkus, M., J. Amer. Chem. Soc., 68, 10 (1946).
[18] Billman, J.H. and Dorman, L.C., J. Pharm. Sci., 51, 1071 (1962).
[19] Hammouda, W.M.S., M. Sc. Thesis, Mansoura University, (2000).
[20] Roman, G., Comanita, E. and Comanita, B., Acta. Chim. Slov., 49, 575-585 (2002).
[21] The Merk Index of Chemicals and Drugs, 9th ed., items No. 2327, 6751, 6753, 8959 and 9037.
[22] Hamama, W.S., Hammouda, M. and Afsah, E.M., Z. Naturforsch., 43b, 483-486 (1988).
[23] Blicke, F.F., Org. Reaet., 1, 303 (1942).
[24] Brewster, J.H., and Eliel, E.L., Org. React., 7, 99 (1953).
[25] House HO, Modern Synthetic Reactions, 2nd ed. (Benjamin. Cummings), California, pp 602-611, (1972).
[26] Al. Shahaby, E.H.A., M. Sc. Thesis, Mansoura University, (2003).
[27] Andrisano, R., Angleoni, A.S., Demaria, P. and Tramontini, M., J. Chem. Soc., [C] 2307 (1967).
[28] Angeloni, A.S., Angiolini, L., De Maria, P., and Fini, A., ibid., [C] 2295 (1968).
[29] Gill, N.S., James, K.B., Lions, F., and Potts, K.T., J. Amer. Chem. Soc., 74, 4923 (1952).