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SYNTHESIS AND SELECTED REACTION OF 9 - (2- CYANOETHYL) -1- OXA- 9 - AZA -TRICYCLO [4.2.1.$0^{2,8}$] NONAN- 3 - ONE - 6 - CARBONITRILE

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ABSTRACT

Oxirination of the activated 3,4 -olefinic double bond of 8-(2-cyanoethyl) -8-azabicyclo [3.2.1] oct -3-en-2-one -6-carbonitrile (1) with basic hydrogen peroxide afforded 9-(2-cyanethyl)-1-oxa-9-azatricyclo [4.2.1.$0^{2,8}$] nonan-3-one-6-carbonitrile (2). Ring opening of the oxirane ring in (2) has been investigated, using 10% sodium hydroxide, acetic acid, and phenylhydrazine to give (4), (7) and (8) respectively. Structural and configurational assignments were deduced from IR, ^{1}HNMR, UV and mass spectral evidence.

INTRODUCTION

The reaction of 3-pyridinol with acrylonitrile and methyl acrylate constitutes simple one pot high yield conversions into complex tropane-like alkaloid, 8-substituted 8-azabicyclo [3.2.1] octenone derivatives[1]. 1,3-Dipolar cycloaddition reactions are reversible thermally, photochemically and electron impact [1,2]. Compounds of the type (1) undergo retro-1,3 - dipolarcycloaddition reactions under thermal conditions to yield 3-pyridinol [1].

The reversibility of such reactions and the availability of the substrate (1) in high yield make those type of compounds as valuable synthetic intermediates. In previous work, we have attempted to exploit such retro-reactins for the synthesis of 4-and 5-methyl-3-pyridinols[2].

However, all attempts to get the key intermediate 2,3-dicarbonyl cycloadduct either by selenium dioxide oxidation or with isoamyl nitrile with the hydrogenated cycloadduct [1] had failed with the view to prepare 3,4-dihydroxypyridine.

Now, we wish to report herein the oxirination of the activated 3,4-olefinic double bond of the substrate (1), 8-(2-cyanoethyl) 8-azabicyclo [3.2.1] oct-3-en-2-one-6-carbonitrile to give 9-(2-cyanoethyl)-1-oxa-9-aza-tricyclo [4.2.1.02,8] nonan-3- one-5-carbonitrile (2), which is considered to be a convenient source of the key intermediate8-(2-cyanoethyl)-3,4-dihydroxy-8- azabicyclo [3.2.1] octane-2-one - 6-carbonitrile required for the synthesis of 3,4-dihydroxy pyridine.

α, β-Unsaturated ketones with peracids usually do not lead to oxirination of the double bond. The reaction with conjugated ethylinic dcuble bond is retarded sufficiently so that the reaction of peracids with carbonyl group usually becomes the predominant process. However, oxirination of α, β-Unsaturated ketones can be accomplished directly by nucleophilic reagents such as sodium salt of hydrogen peroxide.

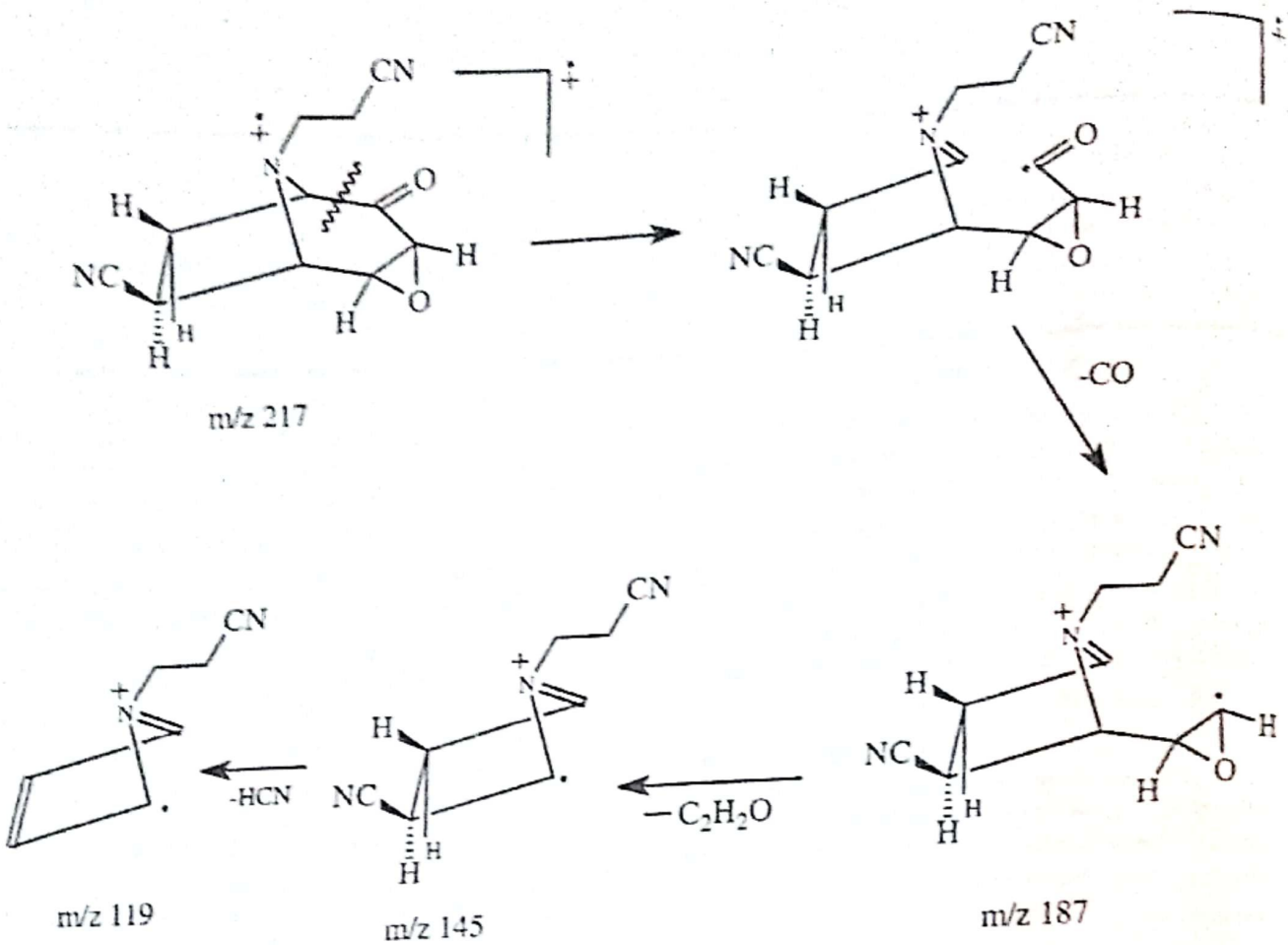
Thus, 8-(2-cyanoethyl)8-azabicyclo [3.2.1] oct-3-en-2-one -6-carbonitrile (1) has been oxirinated by hydrogen peroxide in 5% sodium hydroxide at room temperature. The oxirane obtained (2) was characterized by means of periodate test [3-7], and spectral evidence.

IR spectrum of (2) displayed streteching frequency characteristic of non-conjugated carbonyl group at 1720 cm^{-1} and C ≡ N at 2225 cm^{-1}. The stretching frequencies characteristic of the olefinic C-H and the conjugated olefinic double disappeared. The u.v absorption band at λ 224.5 nm which is characteristic of the enone chromophors [8] in (1) also disappeared in (2).

The structure of (2) was derived from ^{1}HNMR and mass spectral analyses. The ^{1}HNMR spectrum of (2) displayed ufield shielded protons and lack the downfield 3,4-vinylic protons. 5.4 (H-4,d,$J_{4,2\text{-}\underline{endo}}$ = 2 Hz, $J_{4.5\text{-}\underline{exo}}$ = 5Hz, $J_{4.5\text{-}\underline{endo}}$ = 10Hz); 3.5 (H-2, dd, $J_{4,2\text{-}\underline{endo}}$ = 2 Hz, $J_{2\text{-}\underline{endo}}$ -8- endo = 8 Hz); 5.1 (H-8, dd, $J_{8,2}$ = 8 Hz , $J_{8,7}$ = 6Hz); 5.8 (H-7, d,$J_{7,8\text{-endo}}$ - = 5Hz, J 7,6-endo is small enough to be neglected); 3.9 (H-6,m); 2.98(H-5-exo-over-lapped with the other signal); 2.1 (H-5- <u>endo</u> J, not measurable owing to signal overlap).

The splitting pattern of H-2 and H-8 as double dculets is compatible with the <u>exo</u>-stereochemistry of the fused oxirane ring. The corresonding endo-oxirane derivative resulting from endo-face attack has not been detected.

The substrate (1) separated as yellou viscous oil using column of alumina had been proved to be inseparable isomeric mixture of 6-endo- and 6-<u>exo</u>- carbonitrilestereoisomers inalmost equal amounts based on ^{1}HNMR evidence (1). However, the exo-configuration of the 6-carbonitrile group in (2) has been assigned from the splitting pattern of H-7 in ^{1}HNMR spectrum. H7 appears as a doublet at 5.8ppm due to negligible $J_{6,7\text{-endo}}$ coupling.



Scheme 1 : FRAGMENTATION OF 9 - (2- CYANOETHYL) -1- OXA- 9 - AZA -TRICYCLO $[4.2.1.0^{2,5}]$ NONAN- 3 - ONE - 6 - CARBONITILE.

The 6-endo-stereoisomer has not been detected. The isolation the oxirane (**2**) has 6-exo-carbonitrile group indicated that epimerisation at charbon-6 had taken place under the influence of sodium hydroxide in the reaction mixture.

This is not surprised since H-6 is acidic enough due to the adjacent electron-withdrawing carbonitrile group. Abstraction of the 6-endo- proton by the hydroxide anion yielded the stabilized carbanion. Recombination with proton gives the more thermodynamically stable 6-exo-carbonitrile steroismoer (**2**).

The mass spectrum of the oxirane (**2**) displayed the expected molecular ion at m/z 217 a.m.u. The following mechanism is suggested for the subsequent fragmentations of the molecular ion in the ionization chamber. (cf. Scheme-1).

The isolation of the oxirane (**2**) in substantial amount lead us to investigate the ring opening of the strained oxirane ring by acetic acid and sodium hydroxide, with the view to get the key intermediate 3,4-glycol.

Thus, treatment of ethanolic solution of (**2**) with 10% aqueous solution of sodium hydroxide at room temperature for 1 h afforded a yellow solid identified as a tautomeric mixture of 3-hydroxy-8-azabicyclo [3.2.1] oct -3-en-2-one-6-exo-carbonitrile (**3**) and 8- (2 cyanoethyl)- 8-azabicyclo [3. 2.1] octan-2,3-dione-6-exo-carbonitrile from elemental analyses and spectral evidence.

The infrared spectrum of the isolated solid exhibited a broad band at 3500-2600 cm^{-1} assignable for the enolic group adjacent to the carbonyl group in which

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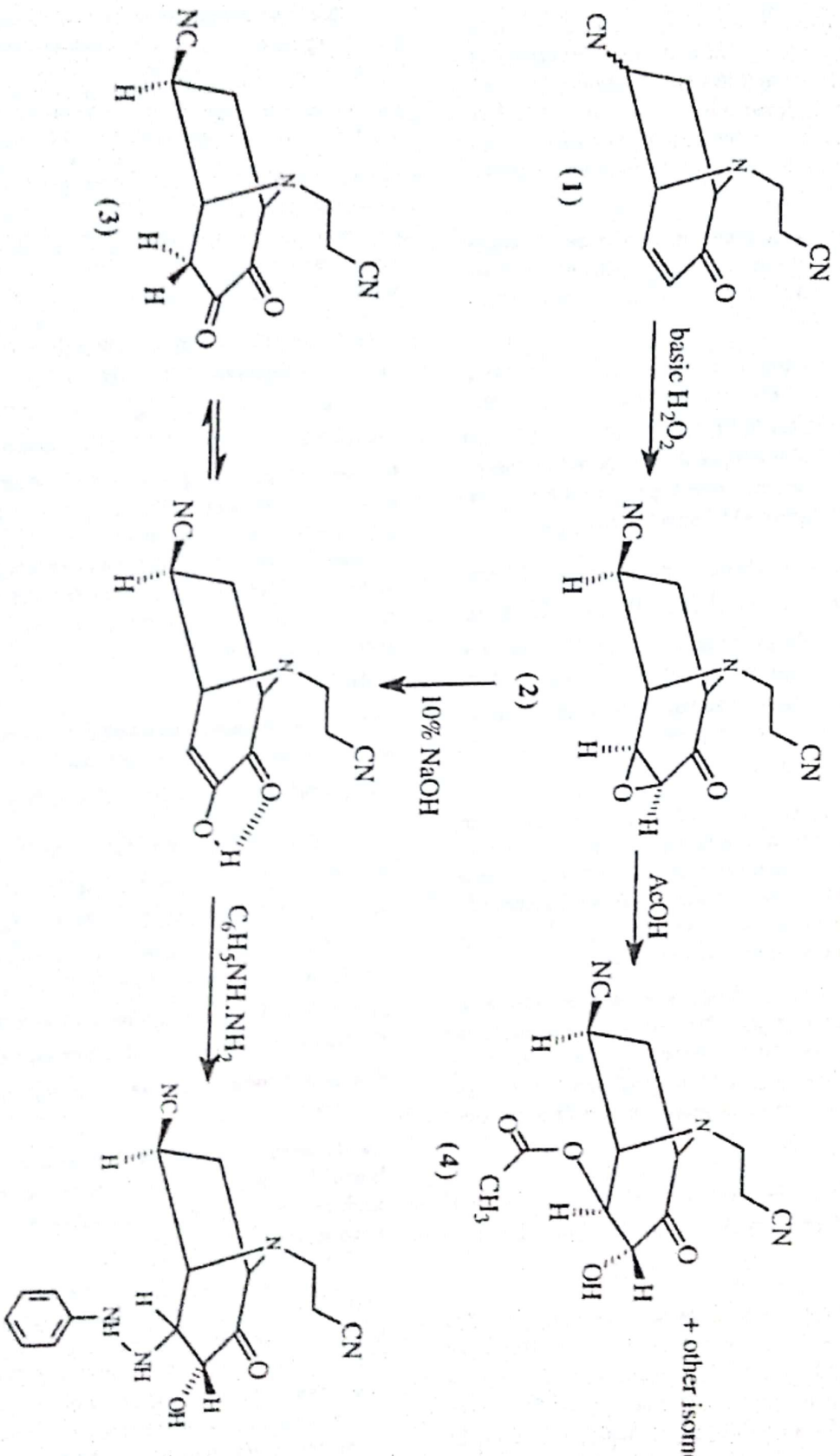

Scheme 2

intramolecular hydrogen bonding is possible. The absorption bands at 1735, 1720 and 1670 cm^{-1} are for diketone, and α, β-unsaturated ketone in (3). The absorption band at 1640 cm^{-1} is for (conjugated C=C). It is suggested that (3) probably formed via elimination of water molecule undeer the influence of sodium hydroxide. H-3 in the non-isolated intermediate glycol H-3 is acidic in which it facilitates the base induced E-2 elimination process leading to (3) together with its diketone-tautomer.

Sublimation of the tautomeric mixture (3) under reduced pressure and n the presence of nitrogen atmosphere has failed due to the decomposition of the substance. (cf. Scheme-2).

On the other hand, phenylhyydrazine in aceticc acid reacted with the tauomeric mixture (3) to give yellow needless, m.p 128-130 ^{o}C, (10%, yield), identifed as 8- (2-cyanoethyl)-3-hydroxy-4- phenylhydrazino-8-azabiccyclo [3.2.1] octan-2-one-6-exo-carbonitrile (5) from elemental analyses and IR spectrum.

The IR exhibited a broad band at 3650-2850 cm^{-1} assignable for polymeric OH and NH group, 2225 cm^{-1} is for the carbonitrile group and 1740 cm^{-1} is for non-conjugated carbonyl group. Skeletal vibrations of aromatic ring apears at 1605, 1540 and 1500 cm^{-1}. Out-of plane bending vibration of monosubstituted phenyl group displayed - C -H at 750 cm^{-1}.

The isolation of (5) indicated that (3) constitutes the major component in tthe tautomeric mixture. Compound (3) appears to be more thermodynamically stable than the diketone tautomer, probably due to the intramolecular hydrogen bonding between hydroxyl group at position-3 with the adjacent carboonyl group.

Analogous treatment of the oxirane derivative (2) with glacial acetic acid gave the hydroxy acetate derivative, identified as 8-(2-cyanoethyl) -4-acetoxy-3-hydroxy -8-azabicyclo [3.2.1] octan-2-one-6-exo- carbonitrile (4) from elemental analysis and spectral evidence.

The IR of (4) exhibited OH at 3480 cm^{-1}, 2220 cm^{-1} C≡N, 1725 cm^{-1} (non-conjugated C=O) and 1715 cm^{-1} (acetate carbonyl).

The ^{1}HNMR spectrum of (4) displayed 5.05 (H-1, dd, J=6 and 8 Hz) 4.5 (H-3, dd, J=6 and 10 Hz), 4.85 (H-4, J=6 and 10, Hz), 5.55 (H-5, d,J=10 Hz. J5,6-endo-, J=8 and is small enough to be neglected), 3.9 (H-6-endo-J=10 Hz), 2.24 (H-7-endo-, J=8 and 14), 2.75 (H-7-exo-, J=8.10 and 14 Hz). Further investigations concerning synthetic applications of the oxirane derivative (2) is currently investigated.

EXPERIMENTAL

Melting points were determined on Gallenkamp melting point apparatus and were uncorrected. I.R spectra were recorded on a Pye-Unicam model SP 300 infrared spectrophotometer (V max in cm^{-1}), PMR spectra in $CDCl_3$ on a Varian EM-390 spectrometer using TMS as an internal reference, (Chemical shifts in δ, ppm). All the compounds were purified by column chromatography over alumina C-neutral (Fluka). Elemental analyses were performed at the University of Ain Shams and were within ±0.4% of the theoritical vaiues.

9- (2-Cyanoethyl)-1-oxa-9-azatricyclo [4.2.1.0^{2,8}] nonane-2-one 6-exo-carbonitrile (2):

8-(2-Cyanoethyl)-8-azabicyclo [3.2.1] oct-3-en-2-one, the substrate (1) was prepared according to Banerji et al [(i)], (5 g, 0.025 mol), was dissolved in ethanol (100 ml), and to this a homogeneous solution of 30% hydrogen peroxide (30 ml) was added. To this mixture (20ml) of 5% aqueous sodium hydroxide was added dropwise while stirring for one hr at room temperature. the reaction mixture was then cooled and poured into about 500 ml of water. It was kept over night at 0 ^{o}C.

The separated oxirane derivative was filtered off and recrystallised from ethanol to give the desired compound m.p 188 - 190 ^{o}C. (40 % yield).

The IR showed 1720 cm^{-1} (non-conjugated (C = O), and 2225 cm^{-1} (C ≡ N). ^{1}H NMR: δ 5.4 (H-4 d, $J_{4,2\text{-endo}}$= 6 Hz, $J_{4,5\text{-exo}}$ =5 Hz, $J_{4,5\text{-endo}}$ = 10 Hz); 3.5 (H-2, dd $J_{4,2\text{-endo}}$ =6Hz, $J_{2\text{-endo},8\text{-endo}}$=8Hz); 5.1 (H-8, dd, $J_{8,2}$=8H, $J_{8,7}$=6H); 5.8 (H-7, d, $J_{7,8\text{-endo}}$=5Hz, $J_{7,6\text{-endo}}$ is negligible); 3.9 (H-6,m); 2.98 (H-5-exo-over-lapped with other signal); 2.1 ppm (H-5-endo,J, not measurable owing to signal overlap). [M^{+}] = 217 am.u.

Tautomeric mixture of 3-hydroxy-8-(2-cyanoethyl)-8-azabicyclo [3.2.1] oct-3-en-2-one-6-exo-carbonitrile and 8-azabicyclo [3.2.1] octane-2,3-dione-6- exo-carbonitrile (3):

Oxirane (2), (1g, 0.0046 mol) in ethanol (15 ml) and 10% aqueous sodium hydroxide (4 ml) were heated under reflux for 1h. The reaction mixture was then poured into ice-cold water, neutralized with 10% hydrochoric acid and then extracted with ether. Ether layer wass separated, washed with water, separated and dried over anhydrous sodium sulphate. Ether was then evaporated on steam-bath, whereupon, a yellow crystalline material was obtained, m.p. 160^{o}C (decomp.) IR 3600-

2600 cm^{-1} (br, OH), 2230 cm^{-1} (C≡N), 1735, 1720 and 1670 cm^{-1} (C=O groupings), 1640 cm^{-1} (conjugateed C=C).

8- (2-Cyanoethyl) -4-acetoxy -3-hydroxy -8- anzabicyclo [3.2.1] octean -2- one -6- exo-carbonitrile (4):

Oxirane derivative (2) (1g, 0.0046 mol) in ethanol (15 ml), and gleaial acetic acid (5 ml) were heated under reflux for 2 h. the reaction mixture was cooled and poured into ice-cold water, and neutralized with sodium bicarbonate solution. The organic material were extracted twice with ether.

The ether was washed with water, separated and dried over anhydrous sodium sulphate. Ether was driven off on steam-bath. The colourless solid obtained was filtered, and recrystallization from ethanol gave (4), m.p 230 ^{o}C (decomp.), (yield, 65%). IR, 3480 cm^{-1}(OH), 2220 cm^{-1} (C≡N), 1725 cm^{-1} (non- -conjugated C=O), and 1715 cm^{-1} (acetate).

8- (2-Cyanoethyl) -3-hydroxy -4- phenylhydrazino 8-azabicyclo [3.2.1] octane -2- one-6- carbonitrile (5):

Tautomeric mixture (3), (1g, 0.003 mol) in ethanol (15 ml) and phenylhydrazine (2ml) in acetic acid (2ml) were heated under reflux for 2h.

The reaction mixture was then poured into ice-cold water. Keep the contents in the fridge overnight. The organic materials were extracted with ether. The ether layer was separated, dried with unhydrous sodium sulphate. Evaporation of ether afforded a bright yellow oil soon solidified as yellow needles m.p. 128-130 oC (70%, yield). IR: 3650-2800 cm^{-1} br., (OH and NH), 2225 cm^{-1} (C≡N), 1740 cm^{-1}(on-conjugated C=O, and 1605, 1540 and 1500 cm^{-1} (phenyl group vib.) and 750 cm^{-1} (- C-H monosubstituted pheyl group).

REFERENCES

1- J.Banerji, .Dennis, J.Frank, A, R. Katritzky and T. Matsuo; **J. Chem. Soc. Perkin I,** 2334 (1976).

2- A.H.Moustafa, S.A.El-Abbady and S.Donia., **Bull. Fac. Scl., Ain Shams University,** Cairo, Egypt, (1983).

3- H.M.Walton, **J. Org. Chem.,** 22, 1161, (1957).

4- Vir. Vatente and J. L. Wolfhangen, **J. Org. Chem.,** 31, 2509 (1966).

5- G.B.Payne and J.H.Williams., **J. Org. Chem.,** 24, 284 (1959).

6- Gorodetsky, N.Danieli and Y.Mazur., **J. Org. Chem.,** 32, 760 (1967).

7- A., H.El-Askalai, S.A.El-Abbady, A. A. Al-Ahmady A.M.Abou El-Magd and A. H.Moustafa., **J. Indian. Chem. Soc.,** 69, 306 (1992).

تشييد وتفاعلات مختارة لمركب ٩-(٢-سيانوايثيل) -١-أكزا-٩-ازا-ترای سيكلو (4.2.1.0) نونان-٣-أون-٦-كاربونيتريل.

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بتأثير محلول قلوى لفوق أكسيد الهيدروجين على ٨-(٢-سيانوايثيل)-٨- أزابای سيكلو (3.2.1) أكتا-٣-ين -٢-اون -٦-كاربونيتريل امكن تشييد الأكزيران المقابل ٩-(٢-سيانوائيل)-١اكزا -٩أزا -ترای سيكلو (0.2.1.0) نونان -٣ - أون -٦ - كاربونيتريل

ولقد تم دراسة فتح حلقة الأكزيران فى هذا المركب بواسطة هيدروكسيد الصوديوم وحمض الخليك وفنيل هيدرازين وتم دراسة التركيب الجزيئى للمراكبات الجديدة المعزولة على ضوء دراسة أطياف الأشعة تحت الحمراء وفوق البنفسجية وطيف الرنين النووى المغناطيس للبروتون وطيف الكتلة. واثبتت هذه الدراسة الأهمية التحضرية الكبيرة فى مجال كيمياء الحلقات غير المتجانسة .