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ACTIVATED NITRILES IN HETEREOCYCLIC SYNTHESIS. NEW ROUTE FOR THE SYNTHESIS OF SPIROISOQUINOLINE DERIVATIVES.

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النتريلات النشطة في تخليق الحلقات الشبه حلقية .

طريق جديد لتخليق مشتقات الإسبيرو أزولينولين .

الخلاصة : في هذا البحث تم تحضير مركب جاما - سيانو - جاما - (٤ - بير يديل) بيميلو نيتريل (٢) بواسطة السيانو اثيليشن لمركب ٤ - بيريديل اسيتو نيتريل (١) ، وبواسطة التحليل المائي لمركب (٢) مستخدما حمض الهيدروكلوريك المخفف أمكن الحصول علي جاما - أميدو - جاما - (٤ - بيريديل) حمض البيميل (٣) حيث يتحولق معطيا ٣ - (٤ - بيريديل) - ٢ ، ٦ - بيريدين داي أون - ٣ - حمض البروبونك (٤) ، وذلك بالتسخين المستمر في محلول حمض الهيدروكلوريك .

ويتم حولقة مركب (٤) في وجود حمض الكبريتيك المركز ليعطي مشتقات الإسبيرو كينولين رقم (٥) ، كذلك تم تحضير بعض مشتقات الأسبيروكينولين من (٦ - ١١) .

وقد تم إثبات التركيب الكيماني للمركبات المحضرة بواسطة التحاليل الدقيقة والتحاليل الطيفية المختلفة .

Abstract-

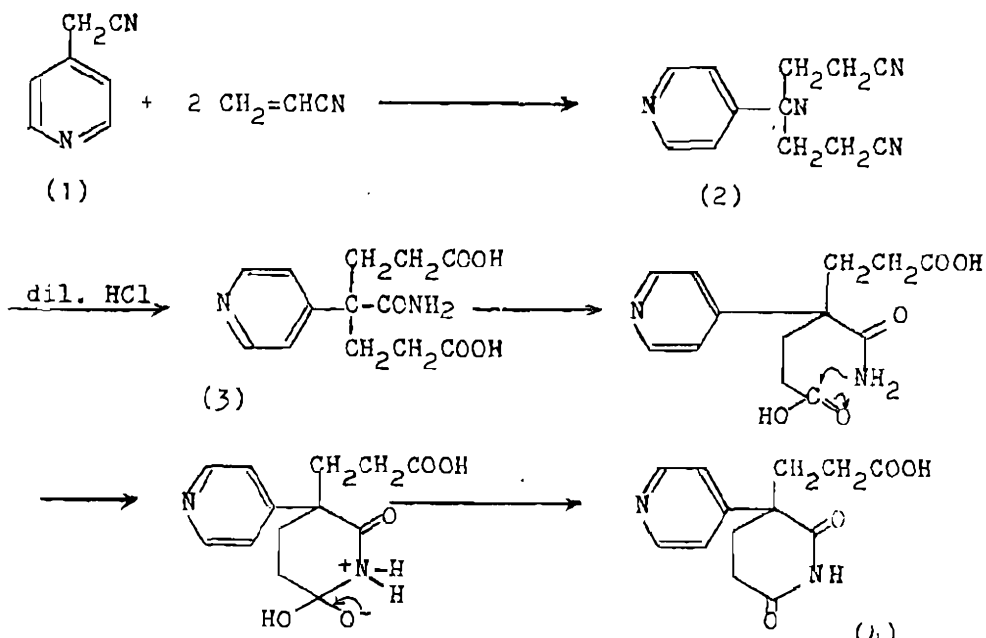
γ-Cyano-γ -(4-pyridyl)pimelonitrile (2) has been prepared by cyanoethylation of 4-pyridyl-acetonitrile (1). Hydrolysis of (2) using dil. HCI afford γ-amido-γ- (4-pyridyl)pimelic acid (3) which cyclized to the corresponding 3 -(4-pyridyl)-2,6-piperidindione-3- propionic acid (4) by continues heating in hydrochloric acid solution. Ring closure of (4) takes place in presence of conc. sulphuric acid to give spiroisoquinoline derivative (5). Spiroisoquinoline derivative (6-11) have been also prepared. Structure of all the products have established by elemental and spectral analysis .

RESULTS AND DISCUSSION

Fadda and co-workers have involved in an expolration of the potentialities of activated nitriles in heterocyclic synthesis 1-4.

Several novel synthesis of azoles , azine and azoloazines might be developed by this work [5,9] . As a part of this programme the reactivity of 4-pyridylacetonitrile (1) towards a variety of reagents has been investigated with the aim of exploring the potentialities of this exceptionally reactive nitrile in heterocyclic synthesis. Thus, it has been found that compound (1) undergoe reaction with acrylonitrile in the presence of alcoholic tetraethylammonium hydroxide solution, cyanoethylation took place through a Michael type addition resulting in the formation of the corresponding trinitriles (2). Hydrolysis of the trinitrile

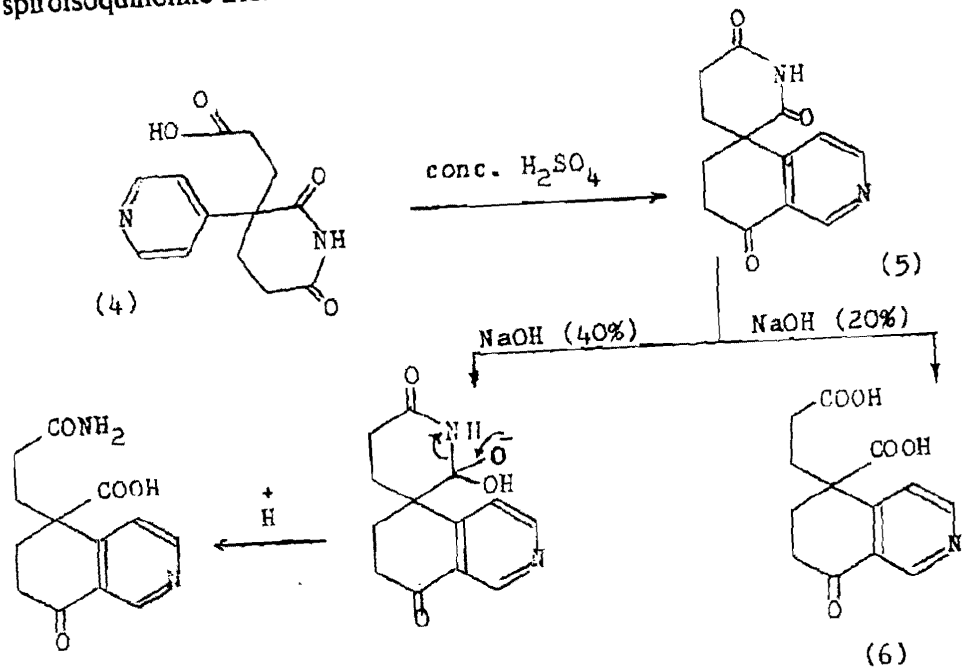
(2) by refluxing with dilute hydrochloric acid for 3 hr afforded γ-amido-γ-(4-pyridyl) pimelic acid (3). Continues heating of (3) for further 10 hr afforded 3-(4-pyridyl)-2,6-piperidinedione-3-propionic acid (4), (probably obtained according to the proposed mechanism, see Scheme 1). The structure of the product (3) was established by elemental analysis and spectral measurements. The infrared spectrum of (3) showed two bands 1700 and 1680 (νCO of COOH, and amidic carbonyl), 3320 (ν OH of COOH) and 3450 cm^{-1} (ν NH_2), while its nmr spectrum showed two triplets at δ 2.6 and 3.1 corresponding to two methylene groups, two singlets at δ 9.3 and 10.3 attributable to NH_2 and COOH protons respectively besides two doublets at δ 7.6-8.5 corresponding to the pyridine protons.



Scheme 1

On the other hand, the IR spectrum of (4) showed two bands 1720 and 1730 (νCO of six-membered cyclic imides), 1700 (νCO of COOH), 2860-3400 (νOH, bonded of COOH) and 3250 cm^{-1} (νNH).

When the piperidine dione derivative (4) was heated with conc. H_2SO_4 acid, ring closure took place with the formation of the spiroisoquinoline trione derivative (5). (scheme 2).



Scheme 2

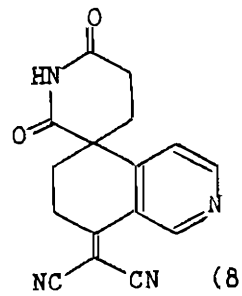
On the other hand, when (5) was subjected to hydrolysis with 20% aq. -NaOH solution, the piperidinedione ring opened and afforded the dicarboxylic acid derivative (7), whereas hydrolysis with 40% KOH solution, gave the acid amide (8).

The preferential attack of the hydroxide ion on the carbonyl group adjacent to the cyclohexanone ring is due to the relatively high electron deficiency on it compared to the other carbonyl group, since in the latter case the positive charge is reduced by hyperconjugation with neighbouring methylene group[10].

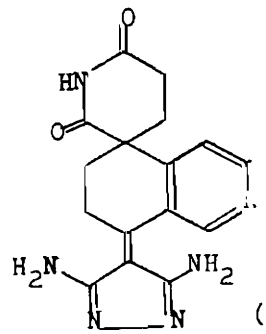
The structures of the products 5-7 were established on the basis of the elmental analysis and IR spectra. The IR spectrum of (5) showed bands at 3240, 3350 and 1750-1690 cm^{-1} characteristic of the stretching frequency of NH, OH, and CO groups respectively, whereas those of (6) showed broad bands at 3320, 1720 and 1700 cm^{-1} attributable to the frequency of OH and CO groups respectively. IR spectrum of (7) exhibited bands at 3450-3350 (NH_2), 3340- (OH), 1720 (CO of COOH) and 1680 cm^{-1} (CO of $CONH_2$ and CO conjugated with aromatic ring).

In addition, it has been found that compound (5) reacted with malononitrile to give the dicyano derivative (8). The dicyanomethylene derivative 8 was used as the key material for the synthesis of, otherwise difficult obtainable, isoquinoline derivatives. Compound (8) was subjected to react with both hydrazine hydrate and/or phenyl hydrazine in equimolar ratio resulted in the formation of the pyrazolo derivatives (9) and (10) respectively. On the other hand, when compound (8) was reacted with thiourea by fusion in presence of TEA afforded the pyrimidinethione derivative (11). Moreover, compound (11) was hydrolysed using ethanolic hydrochloric acid to afford the corresponding pyrimidinedione thione derivative (12) in an excellent yield. Furthermore, compound (12) was also synthesized via another route by the reaction of (5) with thiobarbituric acid in boiling acetic acid containing freshly fused sodium acetate.

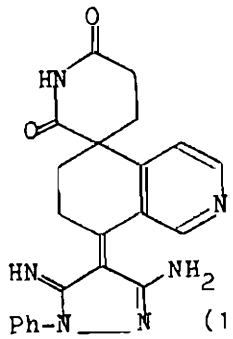
The IR of compounds (9), and (10)showed bands at 3450-3400, 3340-3250 and 1690 cm^{-1} attributable to NH_2, NH, OH, and CO stretching frequencies respectively. While compound 11 showed bands at (1185) cm^{-1} corresponding to the thione group besides the other expected stretching frequencies. ^1H nmr spectrum of (9) showed peaks at 2.4-3.5 (m,8H,4 CH_2), 4.4 (s,NH_2 protons), 7.5-8.5 (pridyl protons) and at 8.8 broad singlet due to NH proton.



(8)



(9)



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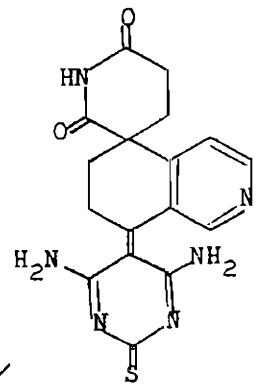

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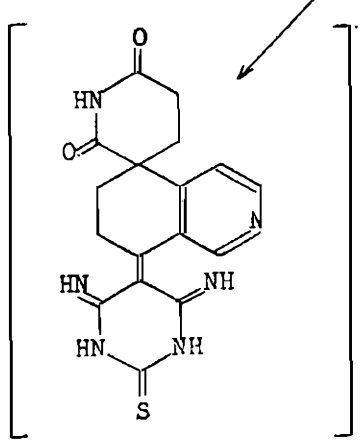
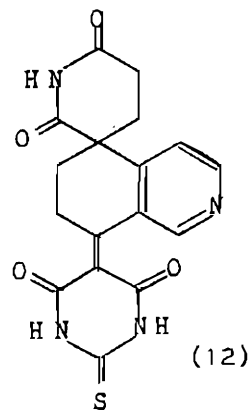
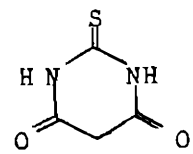


$\overset{+}{H}$, H_2O



(12)



(5) in Ac_2O

EXPERIMENTAL

Melting points are not corrected. The IR spectra (KBr of the prepared compounds were measured on a Pye-Unicam SP 2000 spectrophotometer. PMR spectra were recorded in $CDCl_3$ on Varian EM 360 instrument using TMS as internal standard (chemical shift in δ,ppm).

Synthesis of γ-cyano-γ-(4-pyridyl)pimelonitrile (2):

To a solution of acrylonitrile (0.2 mol) in ethanol (30 ml) was added dropwise a solution of 4-pyridyl acetonitrile (0.1 mol) in ethanol (30 ml) containing a catalytic amounts of tetraethylammonium hydroxide solution (0.5 ml). The reaction mixture was left to stand at room temperature with continuous stirring for 4 hr. Thereafter, the mixture was neutralized with HCl diluted with ethanol, filtered and the obtainable solid mateiral was crystallized from ethanol to give (2). (Table 1).

Formation of γ-amido-γ-(4-pyridyl)-pimelic acid(3):

A solution of (2) (0.1 mol) in water (50 ml) and conc. HCl (30 ml) was refluxed on water bath for 2 hr. The colourless solid separated was filtered, washed well with water and crystallized from water to give (3).

Synthesis of 3-(4-pyridyl)-2,6-piperidinedione-3-propionic acid (4):

A solution of 3 (0.1 mol) in water (50 ml) and conc. HCl (30 ml) was refluxed for 10 hr. The reaction mixture was neutralized with Na_2CO_3 solution. The colourless solid separated was filtered, washed well with water and crystallized from water to give (4).

Synthesis of 5,6,7,8-tetrahydrospiro[isoquinoline-5,3-piperidine]-8,2',6'-triones (5):

A mixture of (4) (0.1 mol) and conc. H_2SO_4 (30 ml) was heated on water bath for 5 hr, cooled, poured slowly on crushed ice with stirring and filtered. The solid thus obtained was washed well with water, suspended in cold water and stirred while adding dil. sodium carbonate solution till the mixture became slightly basic. The product was filtered and recrystallized from acetic acid to give (5) as colourless crystals.

Hydrolysis of (5) with 20% aq. NaOH solution-Formation of 5-carboxylic-8-oxo-5,6,7,8-tetrahydroisoquinoline-5-propionic acid (6):

A solution of 5 (0.1 mol) in 20% NaOH (30 ml) was refluxed for 2 hr. The mixture was cooled and conc. HCl added till acidic when a yellow oil was obtained which solidified on triturating with pet. ether 40-60°. The solid obtained was filtered, washed with cold water and crystallized from water to give (6) as colourless crystals.

Hydrolysis of (5) with 40% aq. NaOH solution. Formation of 5-carboxy-8-oxo-5,6,7,8-tetrahydroisoquinoline-5-propionamide (7):

A suspension of 5 (0.1 mol) in cold water was dissolved by adding a solution of 40% NaOH (10 ml), boiled for 5 min, cooled, acidified with conc. HCl and kept for 7 days in ice chest. The colourless solid thus separated was filtered, washed with water and crystallized from water to give (7).

Reaction of (8) with hydrazines:

A mixture of 8 (0.1 mol) in ethanol (20 ml) and each of hydrazine hydrate or phenyl hydrazine (0.1 mol) was heated under reflux for 2 hr. The reaction mixture was left to cool. The solid products so obtained were

collected by filteration and crystallized from ethanol to give 9 and 10 respectively.

Reaction of (8) with thiourea:

A solid mixture of (8) (0.1 mol), thiourea (0.1 mol) and Et_3N (3 drops) was heated for 20 min. The solid mixture was triturated with ethanol to give (10).

Hydrolysis of (10):

A solution of 11 (0.1 mol) was treated with a mixture of conc. hydrochloric acid (2 ml) and ethanol (20 ml)(was heated for 1 hr. The reaction mixture was allowed to cool and the solid product filtered off and crystallized from ethanol to give (12).

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Table 1. Characterization data of the newly prepared compounds.

Compd. No.	M.P. °C	Yield %	Molecular formula
2	115	60	$C_{13}H_{12}N_4$
3	165	73	$C_{13}H_{16}N_2O_5$
4	247	58	$C_{13}H_{14}N_2O_4$
5	280	71	$C_{13}H_{12}N_2O_3$
6	170	73	$C_{13}H_{13}NO_5$
7	150	61	$C_{13}H_{14}N_2O_4$
8	230	65	$C_{16}H_{12}N_4O_2$
9	261	70	$C_{18}H_{16}N_6O_2$
10	277	75	$C_{22}H_{20}N_6O_2$
11	>300	62	$C_{17}H_{16}N_6SO_2$
12	>300	60	$C_{19}H_{16}N_4SO_4$

a) All elemental analyses (C,H) are in agreement with calculated values.