A STUDY OF THE EFFECT OF NITRO GROUP IN THE SYNTHESIS OF PYRAZOLES AND THIADIAZOLINES FROM HYDRAZIDOYL HALIDES.

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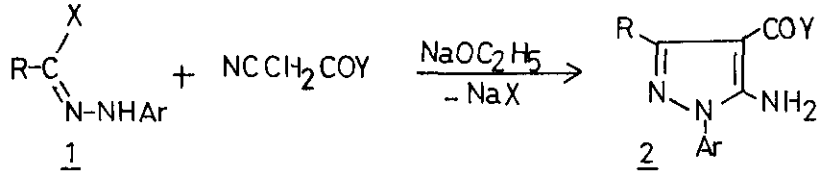
Abstract - The reaction of C-acetyl-N-(2-nitrophenyl)hydrazidoyl chloride 5 with sodium ethoxide and ethyl cyanoacetate yields only one isolable product identified as ethyl 1-(2-nitrophenyl)-3-acetyl-5-aminopyrazole-4-carboxylate 6, in contrast to the C-phenyl-N-(2-nitrophenyl)hydrazidoyl bromide analog 1. The nitrilimine derived from 5 adds to the C=C double bond of the enol tautomers of acetylacetone and dibenzoylmethane and gives the corresponding pyrazole derivatives 7 and 8, which upon hydrazinolysis yield 11 and 12, respectively. These results indicate that the ortho nitro group in 5 seems to have no influence on the course of the reactions of 5 with dipolarophilic reagents. Nucleophilic substitution of the halogen atom in 5 by thiocyanate anion and morpholine seems to proceed in a normal way as other hydrazidoyl halides to give the corresponding thiadiazoline and amidrazone derivatives 13 and 19 respectively.

INTRODUCTION

The reaction of various hydrazidoyl halides 1 (Ar = m-XC_6H_4 or p-XC_6H_4 , or R = alkyl, aryl, ethoxycarbonyl or acyl) with ethyl cyanoacetate and cyanoacetanilide in ethanol in presence of sodium ethoxide has been known to yield 1,3-disubstituted 5-aminopyrazole-4-carboxylic acid derivatives 2[1] (Scheme 1). A recent report by Sunder and Peet[2] has indicated, however, that C-phenyl-N-(2-nitrophenyl)-hydrazidoyl bromide 1 (R = C_6H_5, Ar = 2-$NO_2C_6H_4$, X = Br) reacts with ethyl

cyanoacetate and sodium ethoxide to give 6-bromo-3-phenyl-1.2.4-benzotriazine 3, and 5-bromo-2-phenylbenzoxazole 4 instead of the expected product ethyl 1-(2-nitrophenyl)-3-phenyl-5-aminopyrazole-4-carboxylate 2 (Scheme 1). This finding led us to investigate the reactions of other hydrazidoyl halides having an N-(2-nitrophenyl group) group to cast some light on the effect of the ortho nitro group in the N-aryl moiety on the chemical behaviour of such compounds. This paper discloses the results of our investigation of some reactions of C-acetyl-N-2-nitrophenyl)-hydrazidoyl chloride 5. This compound has not yet been reported although the chemistry of numerous hydrazidoyl halides has been throughly investigated by many authors during the past twenty years[3,4].



1

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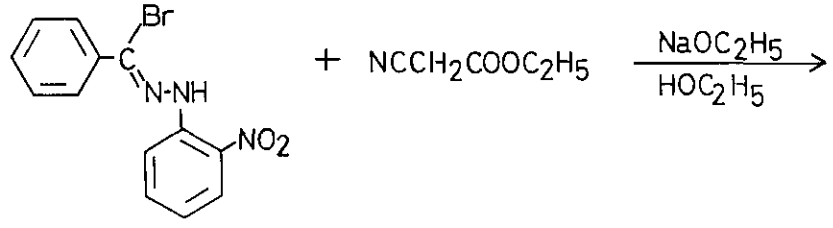
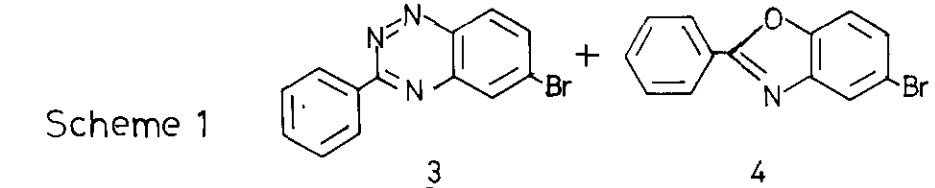
R = alkyl , aryl , acyl , ethoxycarbonyl

X = Cl, Br

Ar= m- or p-substituted phenyl group





3 4

Scheme 1

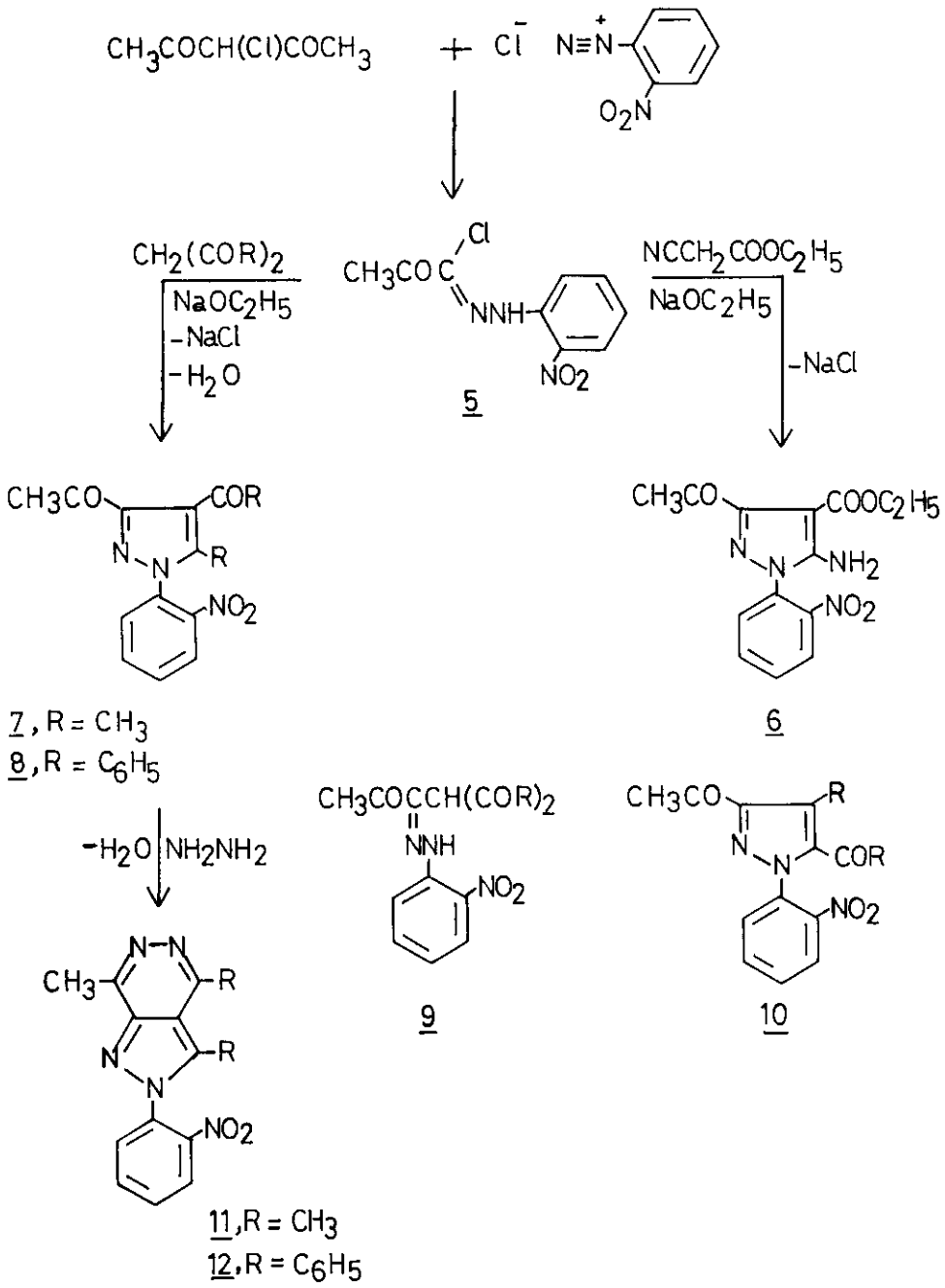
RESULTS and DISCUSSION

Reaction of 5 with sodium salt of ethyl cyanoacetate in ethanol gave a product that was identified as 1-(2-nitrophenyl)-3-acetyl-4-ethoxycarbonyl-5-amino-pyrazole 6. The structure of this product was established on the basis of its spectral and elemental analyses data. Thus, the infrared spectrum (potassium bromide) of 6 reveals bands at 3340 and 3450 cm^{-1} (NH_2) and two carbonyl absorption bands at 1700 and 1670 cm^{-1} assignable to the 3-acetyl and 4-ethoxy-

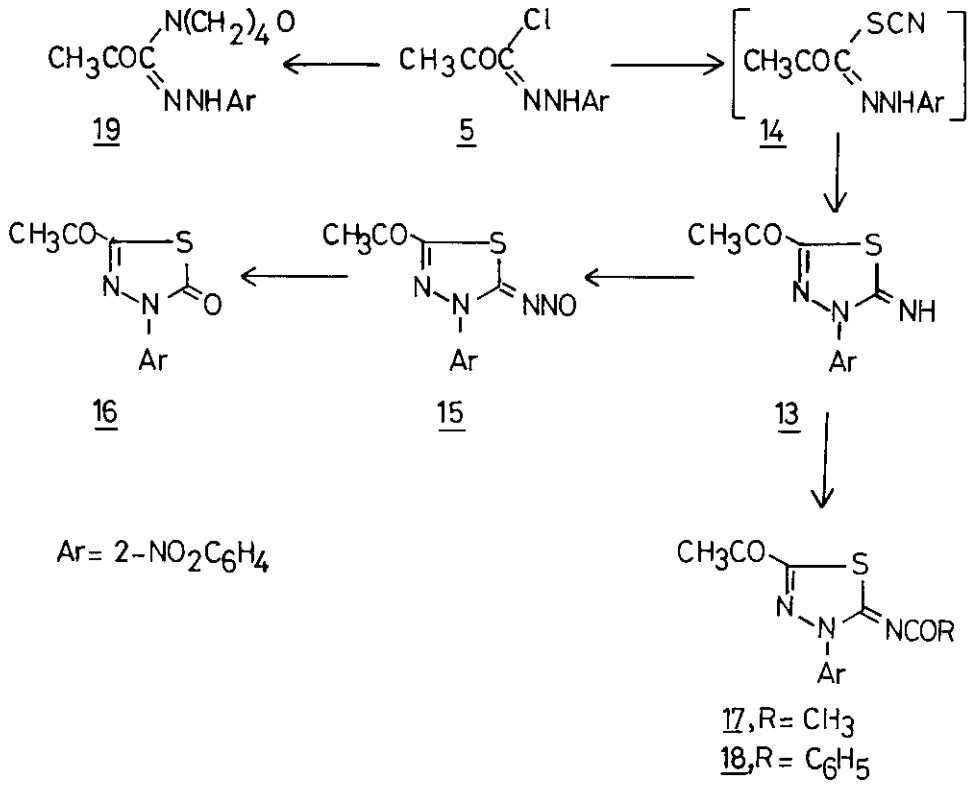
carbonyl groups, respectively. The pmr spectrum of 6 in deuterated chloroform showed signals at δ 5.4 (s, 2H, NH_2), 4.1 (q, 2H, J = 7 Hz, $\underline{CH_2}CH_3$) , 1.3 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$) in addition to the acetyl protons signal near 2.5 (s, 3H) and the aromatic protons multiplet in the region 7.5 - 8.2 ppm. The disappearance of the signal near 5.4 ppm upon exchange with deuterium oxide confirmed its assignment. The mass spectrum revealed the molecular ion peak at m/e 318 with relative intensity 69.3 %. These findings suggest that C-acetyl-N-(2-nitrophenyl)-hydrazidoyl chloride 5, unlike its C-phenyl analog, reacts as other hydrazidoyl halides. This conclusion was further confirmed by its reactions with other dipolarophilic and nucleophilic reagents described below.

Thus, compound 5 reacts with sodium acetylacetonide and dibenzoylmethanide to give the products 7 and 8, respectively. The structures of these products followed their spectroscopic and chemical properties. For example, the electronic absorption spectra of 7 and 8 in ethanol showed, in each case, the characteristic pyrazole absorption maximum[5] in the region 250 - 270 nm and their infrared spectra (potassium bromide) were devoid of ν_{NH} band, thus excluding the open structure of type 9. In addition, the products 7 and 8 failed to give the colour test with alcoholic ferric chloride solution. The other possible isomeric structure 10 was also excluded on the basis that both 7 and 8 react with hydrazine hydrate to give the corresponding pyrazolopyridazines 11 and 12 in good yield, respectively (Scheme 2). The infrared spectra of the latter products showed no carbonyl bands. Also the location of the methyl group on a pyridazine ring carbon atom was evidenced by the downfield shift (2.9 ppm) of the signal of the acetyl methyl (2.6 ppm) at the C_3-position in the corresponding 3-acetylpyrazoles 7 and 8.

On treatment with two equimolar proportions of potassium thiocyanate in refluxing ethanol, the hydrazidoyl chloride 5 was converted into the thiadiazoline derivative 13. Its spectroscopic properties (e.g. absence of SCN stretching at 2165 cm^{-1}) was incompatible with the thiocyanate structure 14 and it was accordingly identified as 2-acetyl-4-(2-nitrophenyl)-5-imino-Δ^2-1,3,4-thiadiazoline 13 (Scheme 3). The latter product was found to be readily nitrosated with sodium nitrite in acetic acid to give the N-nitroso derivative 15, which upon thermolysis looses nitrogen to give 2-acetyl-4-(2-nitrophenyl)-Δ^2-1,3,4-thiadiazolin-5-one 16. Acylation of 13 with acetic anhydride and benzoyl chloride in pyridine yielded the corresponding N-acetyl- and N-benzoyl- derivatives 17 and 18, respectively. The structures of the products 13 and 15 - 18 were supported


CH3COCH(Cl)COCH3
+ Cl⁻
N≡N
O2N
CH2(COR)2
NaOC2H5
-NaCl
-H2O
CH3CO
Cl
C
NNH
NO2
5
NCCH2COOC2H5
NaOC2H5
-NaCl
CH3CO
COR
N
N
R
NO2
7, R = CH3
8, R = C6H5
CH3CO
COOC2H5
NH2
NO2
6
-H2O
NH2NH2
CH3
N-N
R
R
CH3COCCH(COR)2
NNH
NO2
9
CH3CO
R
COR
NO2
10
11, R = CH3
12, R = C6H5

Scheme 2



Scheme 3

by their spectroscopic and elemental analyses data (see experimental section).

Compound 5 was also found to react quite readily with morpholine and a red solid product $C_{13}H_{16}N_4O_4$ was isolated in good yield. Its spectral properties (e.g. its pmr sprctrum shows two pairs of doublets centered at 3.2 and 3.9 ppm) suggest the amidrazone structure 19 (Scheme 3).

Experimental

Spectra were recorded on the following spectrometers - PMR : Varian T-60 spectrometer; MS : Helewett Packed 5980A gas chromatograph spectrometer; IR : Perkin Elmer 257 grating spectrophotometer. Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith lab., Knoxville, Tennessee 37916, USA. α-Chloroacetylacetone was prepared by chlorination of acetylacetone with sulfuryl chloride as previously described[6].

Preparation of C-acetyl-N-(2-nitrophenyl)hydrazidoyl chloride (5) - To a cold well stirred solution of α-chloroacetylacetone (6.7 g, 0.05 mole) and sodium acetate (6.5 g) in ethanol (50 ml) was added an aqueous solution of 2-nitrophenyldiazonium chloride (0.05 mole) dropwise. Stirring was continued for 3 hr after addition was completed. The solid formed was collected and recrystallized from acetic acid to give 5, m.p. 182°C, $C_9H_8ClN_3O_3$, Anal. Found (calcd) C, 44.6 (44.7), H, 3.2 (3.3), N, 17.3 (17.4) and Cl, 14.6 (14.7)%; ir (KBr) 3285 (NH), 1700 (CO), 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ6.6 - 8.0 (m, aromatic), 2.42 (s, 3H, CH_3CO).

Preparation of Pyrazoles (6 - 8) - Into an ethanolic solution of sodium ethoxide prepared from sodium (0.1 g) and absolute ethanol (20 ml) the appropriate active methylene compound (0.005 mole) was added with stirring. To the resulting solution, compound 5 was added. The mixture was stirred for 24 hr and the solid formed was collected and recrystallized from methanol or ethanol. Compound 6: m.p. 134°C, $C_{14}H_{14}N_4O_5$, Anal. Found (calcd) : C, 53.0 (52.8), H, 4.3 (4.4) and N, 17.5 (17.6)%; ir (KBr) 3450, 3340 (NH_2), 1700, 1670 (acetyl CO and ester CO), 1615 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.5 - 8.2 (m, aromatic), 5.4 (s, 2H, NH_2), 4.1 (q, 2H, J = 7.0 Hz, $\underline{CH_2}CH_3$), 2.5 (s, 3H, $COCH_3$), 1.3 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); ms : m/e (rel. int.) 318 (69.3), 273 (26.7), 272 (37.3), 226 (92.0), 77 (28.0), 43 (100.0)%. Compound 7 : m.p. 153°C, $C_{14}H_{13}N_3O_4$, Anal. Found (calcd) : C, 58.3 (58.5), H, 4.5 (4.5), and N, 14.5 (14.6)%; ir (KBr) 1693 (CO), 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.5 - 8.3 (m, aromatic), 2.4 (s, 3H, CH_3), 2.6 (s, 6H, 2 x CH_3CO). Compound 8, m.p. 158°C, $C_{24}H_{17}N_3O_4$, Anal. Found (calcd): C, 70.1 (70.0), H, 4.0 (4.1) and N, 10.1 (10.2)%; ir (KBr) 1690 (CO), 1610 (C=N); pmr ($CDCl_3$) δ 7.0 - 8.0 (m, aromatic), 2.55 (s, 3H, CH_3CO).

Hydrazinolysis of (7) and (8) - A mixture of the appropriate pyrazole derivative (0.005 mole) and hydrazine hydrate (0.01 mole) was refluxed in ethanol (10 ml) for 4 hr. During this period, the pyrazole dissolved and the corresponding pyrazolopyridazine derivatives 11 and 12 precipitated. The product was collected, washed with water and recrystallized from ethanol. Compound 11, m.p. 280°C, $C_{14}H_{13}N_5O_2$, Anal. Found (calcd): C, 59.2 (59.3), H, 4.5 (4.6), and N, 24.8 (24.7)%; ir (KBr) 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 6.8 - 7.5 (m, aromatic), 2.6 (s, 3H, CH_3), 2.9 (s, 6H, 2 CH_3). Compound 12, m.p. 270°C, $C_{24}H_{17}N_5O_2$, Anal. Found (calcd): C, 70.6 (70.7), H, 4.1 (4.2) and N, 17.0 (17.2)%; ir (KBr) 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 6.8 - 7.8 (m, aromatic), 3.1 (s, 3H, CH_3).

Reaction of (5) with potassium thiocyanate - The hydrazidoyl chloride 5 (1.1 g, 0.005 mole) and potassium thiocyanate (1.0 g, 0.01 mole) were refluxed in ethanol (40 ml) for 6 hr, and the hot solution was filtered. The filtrate was cooled, triturated with water and the solid formed was collected. Recrystallization from methanol gave 2-acetyl-5-imino-4-(2-nitrophenyl)-Δ^2-1,3,4-thiadiazoline 13, m.p. 136°C, $C_{10}H_8N_4O_3S$, Anal. Found (calcd): C, 45.2 (45.4), H, 2.9 (3.0), N, 21.0 (21.2) and S, 12.0 (12.1)%; ir (KBr) 3340 (NH), 1685 (CO), 1615 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.2 - 8.1 (m, aromatic), 2.45 (s, 3H, CH_3CO) .

Nitrosation of (13) - A solution of the imino compound 13 (0.5 g) in acetic acid (20 ml) was treated with an equivalent qunatity of sodium nitrite while stirring for 10 min. The reddish product which precipitated was collected, washed with water and recrystallized from ethanol to give 2-acetyl-4-(2-nitrophenyl)-5-N-(nitrosoimino)-Δ^2-1,3,4-thiadiazoline 15, m.p. 140°C, $C_{10}H_7N_5O_4S$, Anal. Found (calcd): C, 40.8 (40.9), H, 2.5 (2.4), N, 23.9 (23.8) and S, 10.7 (10.9)%; ir (KBr) 1700 (CO), 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.6 - 8.4 (m, aromatic), 2.75 (s, 3H, CH_3CO).

Thermolysis of (15) - A solution of 15 (0.2 g) in xylene (20 ml) was refluxed for 10 min. The solvent was then evaporated and the residue was triturated with petroleum ether (40/60). The solid formed was collected and recrystallized from methanol to give 2-acetyl-4-(2-nitrophenyl)-Δ^2-1,3,4-thiadiazolin-5-one 16, m.p. 120°C, $C_{10}H_7N_3O_4S$, Anal. Found (calcd) : C, 45.2 (45.3), H, 2.7 (2.6), N, 15.6 (15.8) and S, 12.1 (12.0)%; ir (KBr) 1700 (CO), 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.55 - 8.20 (m, aromatic), 2.5 (s, 3H, CH_3CO).

Acylation of (13) - Compound 13 (0.5 g) was refluxed in acetic anhydride (20 ml) for 30 min, cooled and poured into cold water. The crude solid which precipitated was collected and recrystallized from acetic acid to give 2-acetyl-4-(2-nitrophenyl)-5-(N-acetylimino)-Δ^2-1,3,4-thiadiazoline 17, m.p. 205°C, $C_{12}H_{10}N_4O_4S$, Anal. Found (calcd) : C, 46.8 (47.0), H, 3.1 (3.2), N, 18.2 (18.3) and S, 10.5 (10.4)%; ir (KBr) 1695 (CO), 1640 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.6 - 8.4 (m, aromatic), 2.3 (s, 3H, CH_3CO), 2.7 (s, 3H, CH_3CO).

Treatment of 13 (0.3 g) with benzoyl chloride (0.7 g) in refluxing pyridine (15 ml) for 20 min, followed by cooling and work up of the reaction mixture gave 2-acetyl-4-(2-nitrophenyl)-5-(N-benzoylimino)-Δ^2-1,3,4-thiadiazoline 18, m.p. 215°C,

$C_{17}H_{12}N_4O_4S$, Anal. Found (calcd) : C, 55.2 (55.4), H, 3.2 (3.2), N, 15.1 (15.2) and S, 8.5 (8.7)%; ir (KBr) 1695 (CO), 1625 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 7.4 - 8.4 (m, aromatic), 2.7 (s, 3H, CH_3CO).

Morpholinolysis of (5) - A mixture of the hydrazidoyl chloride 5 (1.1 g, 0.005 mole) and morpholine (0.8 g, 0.01 mole) was refluxed in ethanol (30 ml) for 30 min and cooled. Dilution with water caused the precipitation of crude *N-(2-nitrophenyl)acetocarbohydrazidoylmorpholine* 19. Recrystallization was effected from methanol to give pure 19, m.p. 130°C, $C_{13}H_{16}N_4O_4$, Anal. Found (calcd) :C, 53.2 (53.4), H, 5.4 (5.5) and N, 19.2 (19.1)%; ir (KBr) 3285 (NH), 1680 (CO), 1610 (C=N) cm^{-1}; pmr ($CDCl_3$) δ 6.9 - 8.3 (m, aromatic), 3.9 (2d, 4H, CH_2OCH_2), 3.2 (2d, 4H, CH_2NCH_2), 2.6 (s, 3H, CH_3CO).

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