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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME PYRROLE DERIVATIVES

Ola A. El-Sayed[1], Hassan M. Mokhtar[2] and Hoda El-Shamy[3]

[1] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy,*
[2] *Department of Chemistry, Faculty of Science,*
[3] *Department of Microbiology, High Institute of Public Health.*
Alexandria University, Alexandria, Egypt

تم فى هذا البحث تحضير العديد من المركبات المحملة علـى ٣-ايثوكسـى كـاربونيل-٢-ميثيـل بيرول-٥-كربوكسالدهيد. بالإضافة إلى تحضير مشتقات البيرازول محملة على نواة البيرول.
وقد تم اثبات التركيب البنائى لهذه المركبات بواسطة التحليل الدقى ودراسة أطيافها فى الأشـعة تحت الحمراء والرنين النووى المغناطيسى.
كما تمت دراسة تأثير هذه المركبات ضد ميكروب سـتافيلوكوكس أوريـس وايشيريشيا كـولاى وكنديدا البيكانس.

Several derivatives have been built up from 3-(ethoxy-carbonyl)-2-methylpyrrole-5-carboxaldehyde. Furthermore, pyrrole-pyrazole derivatives have also been prepared and the antimicrobial activity of all the prepared compounds is reported.

INTRODUCTION

Considerable interest has been focused on pyrrole derivatives which were found to possess a broad spectrum of biological activities[1,2]. Among the most important effects are antibacterial[3], antifungal[4], antispasmodic and analgesic effects[5].

On the other hand, a wide variety of pharmacological properties have been encountered with pyrazole derivatives[6,7]. These observations have prompted the synthesis of compounds containing both pyrrole and pyrazole moieties in order to study their antimicrobial activities.

EXPERIMENTAL

Melting-points were determined in Mel. Temp II apparatus (capillary method) and are uncorrected. The IR spectra were measured in Nujol mull in Beckmann 4210 spectrophotometer. The ^{1}H-NMR spectra were recorded at 60 MHz on a Varian EM-360L spectrometer, in $CDCl_3$ using TMS as internal standard (chemical shift in δ ppm). Elemental analysis were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. The purity of compounds was checked by TLC.

5-(Aryliminomethyl)-3-(ethoxycarbonyl)-2-methylpyrroles (IIa-e)

To a solution of 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde[9] (I) (1.81 g, 0.01 mol) in ethanol (30 ml), the proper amine (0.01 mol) was added with few drops of acetic acid. The reaction mixture was heated under reflux for 3 hr, cooled and poured into cold water. The deposited solid was filtered off, washed with water and recrystallized from ethanol, (Table 1). IR (cm^{-1}): 3300-3250 (NH); 1730-1720 (C=O); 1630-1620, 1600-1570, 1540-1520 (C=N, δ NH, C=C). ^{1}H-NMR for compound (IIa): 1.3 (3H, t, $\underline{CH_3}CH_2$); 2.3 (3H, s, Ar-CH_3); 2.4 (3H, s, pyrrole-CH_3); 4.2 (q, 2H, $CH_3\underline{CH_2}$); 6.85-7.1 (5H, m, Ar-H); 8.15 (1H, s, CH=N); 9.2 (1H, s, NH, deuterium exchangeable).

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Table 1: 5-(Aryliminomethyl)-3-(ethoxycarbonyl)-2-methylpyrroles (IIa-e).

Comp. No.	R	Yield %	M.P. °C	M. formula (M. wt.)	Analysis % (Calcd./Found)		
					C	H	N
IIa	CH_3	70	144-5	$C_{16}H_{18}N_2O_2$ (270.33)	71.09 71.13	6.71 6.81	10.36 10.42
IIb	OCH_3	65	102-3	$C_{16}H_{18}N_2O_3$ (286.33)	67.12 67.12	6.34 6.55	9.78 9.66
IIc	Br	65	147-8	$C_{15}H_{15}BrN_2O_2$ (335.20)	53.75 53.81	4.51 4.60	6.62 6.65
IId	Cl	60	150-1	$C_{15}H_{15}ClN_2O_2$ (290.75)	61.97 62.12	5.20 5.18	9.63 9.50
IIe	SO_2NH_2	80	189.9	$C_{15}H_{17}N_3O_4S$ (335.38)	53.72 53.82	5.11 5.01	12.53 12.61

Table 2: N-Substituted-3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehydes (IIIa-f).

Comp. No.	R	Yield %	M.P. °C	M. formula (M. wt.)	Analysis % (Calcd./Found)		
					C	H	N
IIIa	$COCH_3$	70	134-5	$C_{11}H_{13}NO_4$ (223.23)	59.19 59.23	5.87 5.91	6.27 6.13
IIIb	$COCH_2Cl$	45	108-9	$C_{11}H_{12}ClNO_4$ (257.68)	51.27 51.31	4.69 4.82	5.44 5.54
IIIc	COC_6H_5	50	115-6	$C_{16}H_{15}NO_4$ (285.30)	67.36 67.53	5.30 5.51	4.91 5.11
IIId	CH_3	60	55-6	$C_{10}H_{13}NO_3$ (195.22)	61.53 61.55	6.72 6.93	7.17 7.32
IIIe	CH_2CH_3	65	45-6	$C_{11}H_{15}NO_3$ (209.25)	63.14 63.26	7.23 7.53	6.69 6.81
IIIf	$CH_2C_6H_5$	40	138-9	$C_{16}H_{17}NO_3$ (271.32)	70.83 71.01	6.32 6.53	5.16 5.40

N-Substituted-3-(ethoxycaronyl)-2-methyl-pyrrole-5-carboxyaldehydes (IIIa-f)

Compounds (IIIa-c): To a solution of compound (I) (1.81 g, 0.01 mol) in $CHCl_3$ (6 ml), the substituted acid chloride (0.01 mol) and triethylamine (1.5 ml, 0.011 mol) were added. The reaction mixture was heated under reflux for 1 hr and the solvent was then evaporated under reduced pressure. The residue was digested with water and recrystallized from ethanol, (Table 2). IR (cm^{-1}): 1730 (C=O ester); 1680 (C=O aldehyde); 1625, 1575, 1545, 1505 (C=N, C=C). ^{1}H-NMR of compound (IIIa): 1.2 (3H, t, $\underline{CH_3}CH_2$); 1.7 (3H, s, $COCH_3$); 2.4 (3H, s, pyrrole-CH_3); 4.25 (2H, q, $CH_3\underline{CH_2}$); 7.0 (1H, s, pyrrol C_4-H); 9.3 (1H, s, CHO).

Compounds (IIId-f): To a mixture of compound (I) (1.81 g, 0.01 mol) in acetone (10 ml) and K_2CO_3 (0.5 g) the selected alkyl or aralkyl halide (0.01 mol) was added. The reaction mixture was heated under reflux for 10 hr, filtered off and acetone was evaporated under reduced pressure. The residue was recrystallized from light petroleum (b.p. 60-80°), (Table 2). IR (cm^{-1}): 1730 (C=O ester); 1660 (C=O aldehyde); 1610,1565, 1530 (C=N, C=C). ^{1}H-NMR of compound (IIId): 1.27 (3H, t, $\underline{CH_3}CH_2$); 2.48 (3H, s, pyrrole-CH_3); 3.75 (3H, s, N-CH_3); 4.15 (2H, q, $CH_3\underline{CH_2}$); 7.2 (1H, s, pyrrole C4-H); 9.3 (1H, s, CHO).

N-Substituted-3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde arylhydrazones (IVa-h)

A solution of (I) or (IIId-f) (0.01 mol) and the appropriate arylhydrazines (0.01 mol) in EtOH (10 ml) was heated under reflux for 1 hr, concentrated and the separated product was filtered off and recrystallized from ethanol, (Table 3). IR (cm^{-1}): 3300-3320 (NH); 1735

Table 3: N-Substituted-3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehydes arylhydrazones (IVa-h).

Comp. No.	R	R^1	Yield %	M.P. °C	M. formula (M. wt.)	Analysis % (Calcd./Found)		
						C	H	N
IVa	H	H	60	110-1	$C_{15}H_{17}N_3O_2$ (271.32)	66.40 66.21	6.23 6.52	15.49 15.60
IVb	H	CH_3	72	105-6	$C_{16}H_{19}N_3O_2$ (285.35)	67.35 67.05	6.71 6.91	14.73 14.80
IVc	H	Cl	55	181-2	$C_{15}H_{16}ClN_3O_2$ (305.77)	58.92 59.23	5.27 5.51	13.74 13.81
IVd	H	F	60	116-7	$C_{15}H_{16}FN_3O_2$ (289.31)	62.27 62.36	5.57 5.87	14.52 14.62
IVe	H	SO_2NH_2	80	250-1	$C_{15}H_{18}N_4SO_2$ (318.40)	56.59 56.71	5.70 5.82	17.60 17.91
IVf	CH_3	H	40	109-10	$C_{16}H_{19}N_3O_2$ (285.35)	57.35 57.03	6.71 6.83	14.73 14.52
IVg	CH_2CH_3	H	50	118-9	$C_{17}H_{21}N_3O_2$ (299.38)	68.21 68.03	7.07 7.43	14.04 14.22
IVh	$CH_2C_6H_5$	H	65	151-2	$C_{22}H_{23}N_3O_2$ (361.45)	73.11 73.00	6.41 6.63	11.63 11.81

(C=O); 1620, 1560, 1525 (C=N, δ NH, C=C). ^{1}H-NMR of compound (IVa): 1.34 (3H, t, $\underline{CH_3}CH_2$); 2.25 (3H, s, Ar-CH_3); 2.50 (3H, s, pyrrole-CH_3); 4.24 (2H, q, $CH_3\underline{CH_2}$); 6.46 (1H, s, pyrrole-C_4-H); 6.75-7.35 (5H, m, Ar-H); 9.00 (1H, s, NH; deuterium exchangeable).

Ethyl 1-aryl-3-[N-substituted-3-(ethoxycarbonyl)-2-methylpyrrol-5-yl]-5-methyl (1H) pyrazole-4-carboxylates (Va-g)

Compounds (IVa-h) (0.04 mol), ethyl acetoacetate (31.2 g, 0.24 mol) and dry zinc chloride (5.0 g) were heated to reflux. After part of the ethyl acetoacetate had been distilled off, the temperature was raised to 170°C and kept for 5 min. The excess ethyl acetoacetate was removed in vacuo. The remaining deep reddish-brown residue was recrystallized from ethanol, (Table 4).

^{1}H-NMR of compound (Va): 1.34 (6H, t, $2\underline{CH_3}CH_2$); 2.50 (6H, two overlapping s, pyrrole-CH_3 and pyrazole-CH_3); 4.25 (4H, q, $2CH_3\underline{CH_2}$); 7.1-7.45 (6H, m, Ar-H), 11.30 (1H, s, NH, deuterium exchangeable).

3-(Ethoxycarbonyl)-5-formyl-2-methylpyrrole-oxime (VI)

Hydroxylamine hydrochloride (2.0 g, 0.029 mol) in water (5 ml) was rendered just alkaline with aqueous sodium hydroxide solution (4M). Compound (I) (1.81 g, 0.01 mol) in ethanol (70 ml) was added and the solution was heated under reflux for 1 hr. The mixture was cooled poured into ice-water (Ca. 100 ml) and made acidic with aqueous HCl (4M). The deposited product was filtered off, washed with H_2O, dried and recrystallized from ethanol. Yield 90%. M.P. 153-4°C, $C_9H_{12}N_2O_3$ (196.21).

	C	H	N
Calcd.	55.09	6.16	14.28
Found	55.10	6.00	14.00

IR (cm^{-1}): 3250 (OH), 1725 (C=O). ^{1}H-NMR: 1.28 (3H, t, $\underline{CH_3}CH$); 2.40 (3H, s, pyrrole-CH_3); 4.13 (2H, q, $CH_3\underline{CH_2}$); 6.49 (1H, s, pyrrole C_4-H); 7.7 (1H, s, CH=N); 9.65-9.9 (2H, br. s, NH and OH, deuterium exchangeable).

1-Acetyl-5-cyano-3-(ethoxycarbonyl)-2-methylpyrrole (VII)

A mixture of the foregoing oxime (VI) (0.392 g, 0.002 mol) and acetic anhydride (8 ml) was heated under reflux for 2 hr. The solution was then cooled, poured into water and made alkaline with aqueous NaOH (4M). After 1 hr the precipitate was filtered off, washed with water and recrystallized from ethanol. Yield 66%. M.P. 109-10°C, $C_{11}H_{12}N_2O_3$ (220.23).

	C	H	N
Calcd.	59.99	5.49	12.72
Found	60.12	5.80	12.61

IR (cm^{-1}); 2930 (NH), 2225 (CN), 1720 (C=O), 1560, 1500 (C=N, C=C), ^{1}H-NMR (DMSO-d_6): 1.25 (3H, t, $\underline{CH_3}CH_2$); 1.7 (3H, s, $COCH_3$); 2.47 (3H, s, pyrrole-CH_3); 4.15 (2H, q, $CH_3\underline{CH_2}$); 7.0 (1H, s, pyrrole-C_4-H).

5-(Aminomethyl)-3-(ethoxycarbonyl)-2-methyl-pyrrole (VIII)

Method I: Aluminum metal (2.2 g, 0.082 mol) cut into small pieces (2 cm^2), was left in direct contact with 5% aqueous (distilled water) mercuric chloride solution (40 ml) for 10 min. to induce complete amalgamation. The formed amalgam was washed, by decondition with distilled water (3x10 ml) and rapidly treated with a solution (50 ml) of the oxime (VI) (7.84 g, 0.04 mol) in dilute ethanol (1:1). The reaction mixture was stirred at room temperature for 48 hr, filtered off and the residue washed with ethanol (2x20 ml). The combined filtrate and washings were evaporated under reduced pressure and the residue extracted with ether. The ethereal extract was dried with anhydrous sodium sulphate and evaporated to leave the amine as oil which was used as such for the next step. Yield 55%. ^{1}H-NMR 1.3 (3H, t, $\underline{CH_3}CH_2$); 2.5 (3H, s, pyrrole-CH_3); 3.8 (2H, br. s, NH_2, deuterium exchangeable); 4.24 (2H, q, $CH_3\underline{CH_2}$); 4.85 (2H, t, $\underline{CH_2}NH_2$); 7.1 (1H, s, pyrrole C_4-H); 10.00 (1H, br. s, NH, deuterium exchangeable).

Method II: To a solution of (VII) (2.2 g, 0.01 mol) in absolute ethanol (100 ml), sodium (5 g) was added in portionwise. When the reaction

Table 4: Ethyl 1-aryl-3-[N-substituted-3-(ethoxycarbonyl)-2-methylpyrrol-5-yl]-5-methyl(1H) pyrazole-4-carboxylates (Va-g).

Comp. No.	R	R^1	Yield %	M.P. °C	M. formula (M. wt.)	Analysis % (Calcd./Found)		
						C	H	N
Va	H	H	40	213-4	$C_{21}H_{23}N_3O_4$ (381.44)	66.13 66.00	6.08 6.21	11.02 11.10
Vb	H	Cl	60	216-7	$C_{21}H_{22}ClN_3O_4$ (415.88)	60.65 60.56	5.33 5.51	10.10 10.21
Vc	H	F	65	174-5	$C_{21}H_{22}FN_3O_4$ (399.43)	63.15 63.37	5.55 5.72	10.52 10.61
Vd	H	SO_2NH_2	70	216-7	$C_{21}H_{24}N_4O_6S$ (460.51)	54.77 54.52	5.25 5.36	9.12 9.06
Ve	CH_3	H	82	291-2	$C_{22}H_{25}N_3O_4$ (395.46)	66.82 66.71	6.37 6.56	10.63 11.00
Vf	CH_2CH_3	H	70	183-4	$C_{23}H_{27}N_3O_4$ (409.49)	67.46 67.23	6.65 6.84	10.26 10.03
Vg	$CH_2C_6H_5$	H	35	177-8	$C_{28}H_{29}N_3O_4$ (471.56)	71.32 71.51	6.20 6.42	8.91 9.31

Table 5: 5-(Arylideneiminomethyl)-3-(ethoxycarbonyl)-2-methylpyrroles (Xa-d).

Comp. No.	R	Yield %	M.P. °C	M. formula (M. wt.)	Analysis % (Calcd./Found)		
					C	H	N
Xa	H	65	142-3	$C_{16}H_{18}N_2O_2$ (270.33)	71.10 71.00	6.71 6.82	10.36 10.72
Xb	Cl	70	165-6	$C_{16}H_{17}ClN_2O_2$ (304.78)	63.05 63.10	5.62 5.64	9.19 9.42
Xc	F	45	131-2	$C_{16}H_{17}FN_2O_2$ (288.32)	66.65 66.64	5.94 5.62	9.72 9.94
Xd	NO_2	55	204-5	$C_{16}H_{17}N_3O_4$ (315.33)	60.95 61.14	5.43 5.82	13.33 13.62

mixture was complete after 3 hr, water was added, extracted with ether and worked up as in method I. Yield 35%.

1-Acetyl-5-(acetylaminomethyl)-3-(ethoxy-carbonyl)-2-methylpyrrole (IX)

The foregoing amine (VIII) was heated with acetic anhydride (2 ml) for 2 hr. The reaction mixture was cooled and poured into crushed ice. The yellow crystals separated out were collected and purified by recrystallization from ethanol. M.P. 196-7°C. $C_{12}H_{18}N_2O_4$ (254.29).

	C	H	N
Calcd.	56.68	7.13	11.02
Found	56.88	7.24	11.22

5-(Arylideneiminomethyl)-3-(ethoxycarbonyl)-2-methylpyrroles (Xa-d)

To a sol. of compound (VIII) (1.82 g, 0.01 mol) in ethanol (20 ml), the proper substituted benzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hr, cooled and poured into water. The deposited solid was filtered off, washed with water and recrystallized from ethanol (Table 5). ^{1}H-NMR of compound (Xb): 1.16 (3H, t, $\underline{CH_3}CH_2$); 2.37 (3H, s, pyrrole-CH_3); 4.45 (2H, s, $\underline{CH_2}N$); 4.13 (2H, q, $CH_3\underline{CH_2}$); 7.0 (1H, s, pyrrole-C_4-H); 7.95-8.35 (5H, m, Ar-H); 9.0 (1H, s, NH, deuterium exchangeable).

RESULTS AND DISCUSSION

Chemistry

On 3-ethoxycarbonyl-2-methyl pyrrole-5-carboxaldehyde[9] (I), a variety of ring substituents could be constructed around 1-and 5-position.

Aryliminomethyl derivatives (IIa-e) and arylhydrazones (IVa-h) have been prepared through condensation of aldehyde (I) with various aromatic amines arylhydrazines respectively. Acylation or alkylation of compound (I) afforded N-substituted derivatives (IIIa-f) with free aldehydic group. Moreover, the prepared arylhydrazones (IVa-h) underwent cyclization with ethyl acetoacetate and $ZnCl_2$[10] to produce different pyrazole derivatives (Va-g) (Scheme 1).

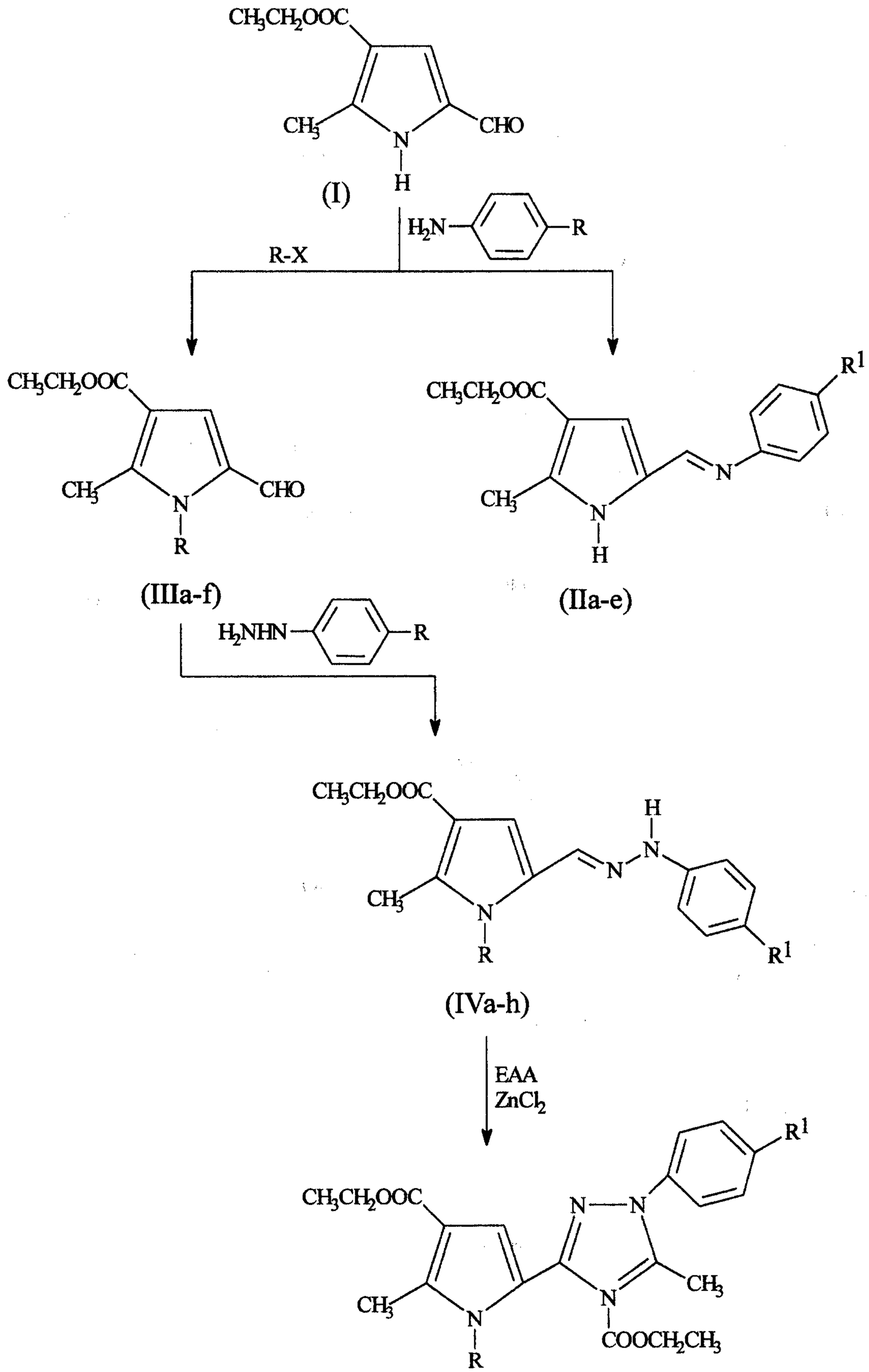
The oxime (VI) obtained by conventional method[11] form formylpyrrole, lost the elements of water upon treatment with acetic anhydride to yield the nitrile of structure (VII). Reduction of (VII) with sodium/ethanol[12,13] furnished the product (VIII) which was identical with the compound obtained from direct reduction of oxime (VI) with sodium amalgam[14]. The only possible structure for that compound (VIII) was therefore the novel 5-aminomethyl-3-ethoxycarbonyl-2-methylpyrrole. The foregoing amine was obtained as a yellowish-brown oil and its structure was confirmed by ^{1}H-NMR spectra. Furthermore, it was identified as its N-aceytl derivatives (IX). In addition, different Schiff's bases (Xa-d) have been prepared by condensation of (VIII) with various aromatic aldehydes (Scheme 2).

Preliminary antimicrobial testing

The preliminary antimicrobial testing of the prepared compounds has been performed by agar diffusion method[8]. *Staphylococcus aureus, E. Coli* and *Candida albicans* are used example of Gram-positive, Gram-negative bacteria and fungi respectively.

The tested compounds and standards were dissolved in dimethylformamide (1 mg/ml). Ampicillin, Canstan and Chloramphenicol were used as standards for *Staph. aureus, Candida albicans* and *E. coli* respectively. All compounds were found less active than standards against the tested organisms.

The results shown, compound (Vc) has antimicrobial activity against *E. coli* with MIC= 0.02 mgm while compounds (Vf), (IVc) and (IVd) are active against *Staph. aureus* with MIC= 0.0025, 1.1 mgm respectively while compounds (IIIf), (IVh) exhibit antifungal activity against *Candida albicans* with MIC of 0.01 mgm.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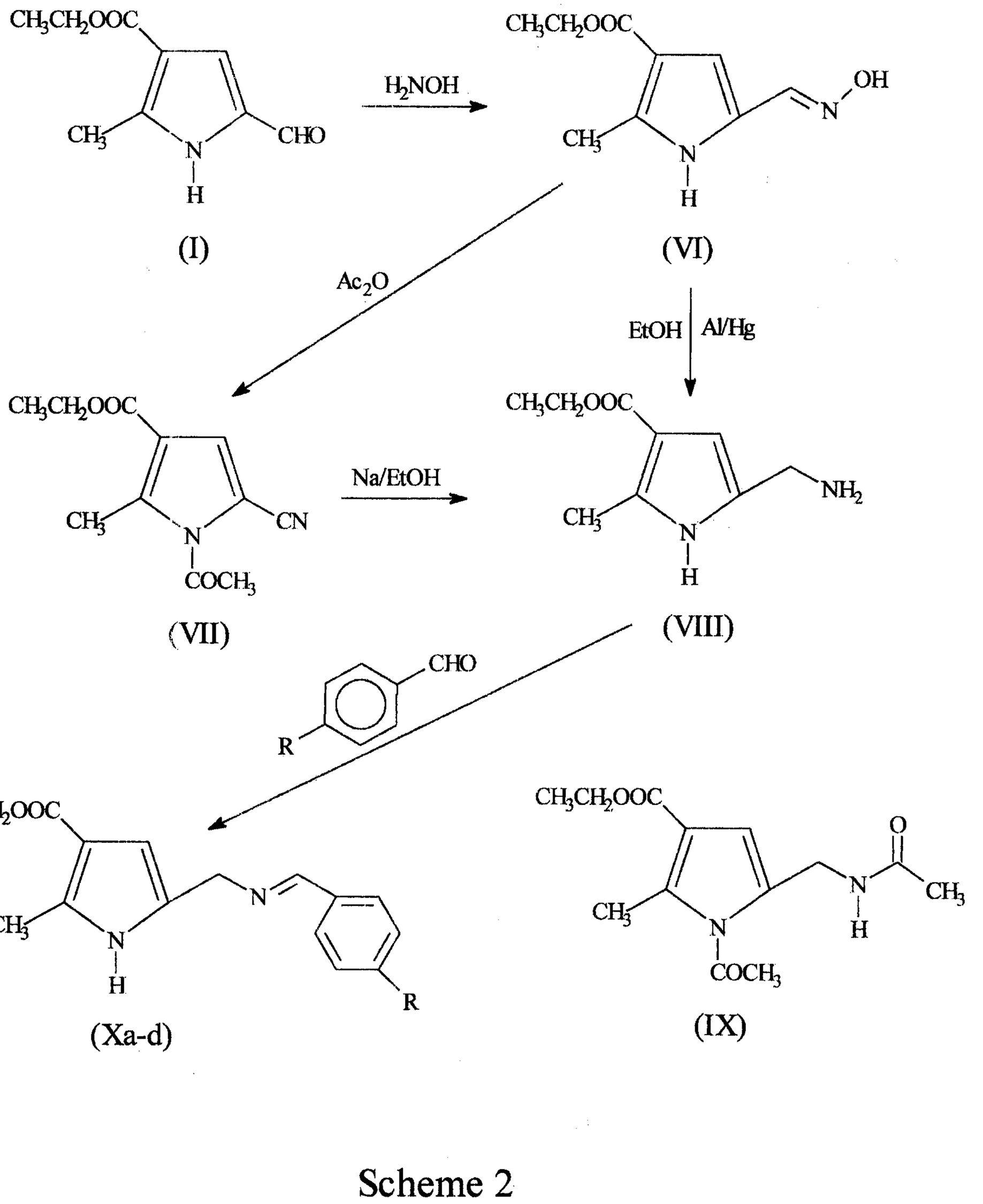
CH3
N
H
CHO
(I)
H2N
R
R-X
R1
(IIIa-f)
(IIa-e)
H2NHN
(IVa-h)
EAA
ZnCl2
(Va-g)

Scheme 1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N
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(I)
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CH3
N
H
OH
N
(VI)
Ac2O
EtOH
Al/Hg
CH3CH2OOC
CH3
N
COCH3
CN
(VII)
Na/EtOH
CH3CH2OOC
CH3
N
H
NH2
(VIII)
CHO
R
CH3CH2OOC
CH3
N
H
N
R
(Xa-d)
CH3CH2OOC
CH3
N
COCH3
N
H
O
CH3
(IX)

Scheme 2

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