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Synthesis of 4-Substituted Aminobenzoate Quaternary Salts as Potent Antispasmodic Agents

EL SEBAI A. IBRAHIM, RAAFAT SOLIMAN ˣ, and MOHAMED GABR

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Abstract □ *N*-(Diethylaminoethyl)-4-substituted aminobenzoate quaternary salts, *N*-(diethylaminoethyl)-4-substituted aminobenzamide quaternary salts, 4-substituted acylaminobenzamide quaternary salts, and 4-substituted acylaminosalicylamide derivatives were prepared and tested for antispasmodic activity. Preliminary pharmacological tests on isolated guinea pig ileum revealed that the new compounds possess nonspecific inhibitory action on smooth muscles.

Keyphrases □ Aminobenzoic acid derivatives—quaternary salts synthesized, antispasmodic activity evaluated □ Quaternary salts—of aminobenzoic acid derivatives synthesized, antispasmodic activity evaluated □ Antispasmodic activity—quaternary salts of various aminobenzoic acid derivatives evaluated □ Structure–activity relationships—quaternary salts of aminobenzoic acid derivatives evaluated for antispasmodic activity

Studies based on the empirical structural scission of the atropine molecule indicated that it did not have a highly specific action. The tropine moiety is a complex amino alcohol that can be simplified but still retain the antispasmodic activity.

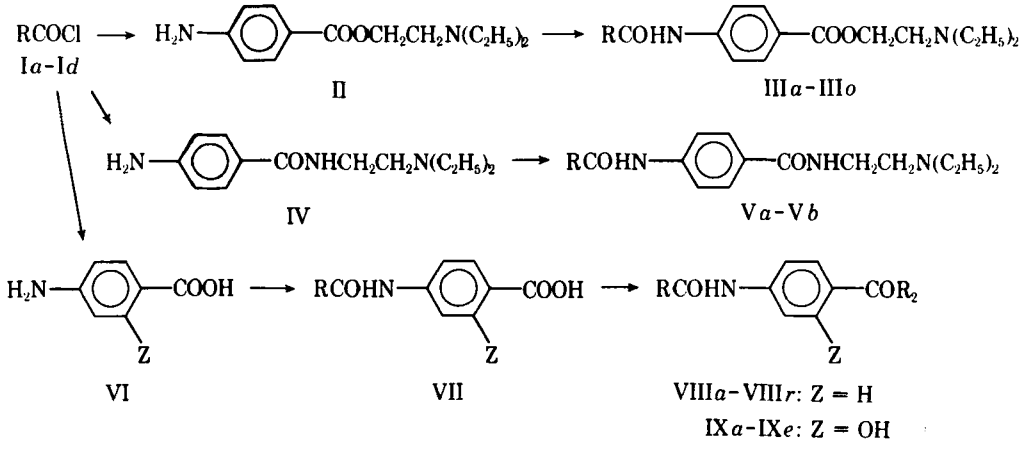
Many parasympatholytic drugs possess potent antispasmodic activity and show some structural resemblance to acetylcholine; at least a tertiary nitrogen atom is needed for activity. Moreover, quaternization of some antispasmodics resulted in significant variations in activity, including enhancement, duration, and toxicity.

The discovery of smooth muscle relaxant properties among many *N*-substituted 4-aminobenzoate esters and amides (1, 2) inspired the preparation of some analogs derived from 4-aminobenzoic and 4-aminosalicylic acids.

The present paper reports the synthesis of some *N*-(diethylaminoethyl)-4-substituted aminobenzoate quaternary salts, *N*-(diethylaminoethyl)-4-substituted aminobenzamide quaternary salts, 4-substituted acylaminobenzamide quaternary salts, and 4-substituted acylaminosalicylamide derivatives and their evaluation for antispasmodic and/or cardiovascular effects.

RESULTS AND DISCUSSION

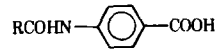
Synthesis—The key intermediates, 4-substituted acylaminobenzoyl chlorides (I*a*–I*d*, Table I), were prepared by the classical method using thionyl chloride and the appropriate acid. *N*-(Diethylaminoethyl)-4-substituted aminobenzoate derivatives (III*a*–III*o*, Scheme I and Table II) were prepared by: Method A, condensation of the appropriate acid



Scheme I

0022-3549/79/0300-0332$01.00/0

Table I—Acyl 4-Aminobenzoic Acids



Compound	R	Yield, %	Melting Point[a]	Formula	Analysis, %	Calc.	Found
Ia	2-ClC_6H_4	72	262–263°	$C_{14}H_{10}ClNO_3$	C	61.0	60.6
					H	3.6	3.3
					Cl	12.9	13.1
					N	5.1	5.1
Ib	3-ClC_6H_4	78	267–268°	$C_{14}H_{10}ClNO_3$	C	61.0	61.2
					H	3.6	3.9
					Cl	12.9	13.3
					N	5.1	4.6
Ic	4-ClC_6H_4	76	270–272°	$C_{14}H_{10}ClNO_3$	C	61.0	60.7
					H	3.6	3.4
					N	5.1	4.7
Id	1-Naphthyl	85	275–277°	$C_{18}H_{13}NO_3$	C	74.1	74.1
					H	4.5	5.0
					N	4.8	5.0

[a] All compounds were crystallized from ethanol.

chloride with procaine hydrochloride in cold aqueous sodium carbonate solution; Method B, condensation of the appropriate acid chloride with procaine hydrochloride in dry benzene in the presence of sodium bicarbonate; or Method C, condensation of the appropriate acid with procaine base in chloroform solution using dicyclohexylcarbodiimide.

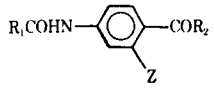
N-(Diethylaminoethyl)-4-substituted aminobenzamide derivatives (V*a* and V*b*, Scheme I and Table II) were prepared similarly using Methods A, B, and D, which involve treatment of procainamide with the appropriate acid chloride in dry pyridine. 4-Substituted acylaminobenzamide derivatives (VIII*a*–VIII*r*, Scheme I and Table II) were prepared using Methods B and D. The compounds were quaternized using ethyl iodide in dry ether. 4-Substituted acylaminosalicylamide derivatives (IX*a*–IX*e*, Scheme I and Table II) were prepared using Method B.

The structures were substantiated by IR, PMR, and mass spectrometric studies of representative members of the series.

Pharmacology—Testing of the antispasmodic activity (3) of III*c*, III*e*, III*g*, V*a*, V*g*, and IX*c* was carried out on isolated guinea pig ileum. All compounds tested inhibited contraction produced by standard submaximal doses of acetylcholine, histamine, or serotonin, with no specificity toward any of these spasmogens. The results showed that the tested compounds might possess considerable nonspecific inhibitory action on smooth muscles similar to that of procaine hydrochloride.

A comparative study of III*c*, III*e*, III*g*, V*a*, V*g*, and IX*c* with a similar molar concentration of procaine hydrochloride was then conducted. All tested compounds were more potent smooth muscle relaxants than procaine, as shown by their antagonistic effects on acetylcholine-induced contractions (Table III).

Table II—4-Substituted Acylaminobenzoate Derivatives



Compound	R_1	R_2	Z	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
III*a*	C_6H_5	$OCH_2CH_2N(C_2H_5)_2$	H	65	78° [a]	$C_{20}H_{24}N_2O_3$		—	—
III*b*	C_6H_5	$OCH_2CH_2N(C_2H_5)_3I$	H	55	176–177° [b]	$C_{22}H_{29}IN_2O_3$	C	53.2	53.2
							H	5.9	5.5
							N	5.6	5.7
III*c*	2-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_2$	H	65	130–131° [c]	$C_{20}H_{23}ClN_2O_3$	C	64.1	63.7
							H	6.2	6.3
III*d*	2-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_3I$	H	60	178–179° [d]	$C_{22}H_{28}ClIN_2O_3$	C	49.8	50.2
							H	5.3	5.2
							N	5.3	5.5
III*e*	3-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_2$·HCl	H	70	187–188° [c]	$C_{20}H_{24}Cl_2N_2O_3$	C	58.4	58.6
							H	5.9	5.5
							Cl	17.2	17.6
							N	6.8	6.8
III*f*	3-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_3I$	H	80	180–181° [e]	$C_{22}H_{28}ClIN_2O_3$	C	49.8	49.8
							H	5.3	4.8
							N	5.3	5.0
III*g*	4-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_2$	H	65	145–146° [f]	$C_{20}H_{23}ClN_2O_3$	C	64.1	64.3
							H	6.2	5.8
							Cl	9.5	9.4
							N	7.5	7.9
III*h*	4-ClC_6H_4	$OCH_2CH_2N(C_2H_5)_3I$	H	78	194–196° [e]	$C_{22}H_{28}ClIN_2O_3$	C	49.8	50.2
							H	5.3	5.7
							N	5.3	5.2
III*i*	$C_6H_5CH_2$	$OCH_2CH_2N(C_2H_5)_2$ picrate	H	54	141–142° [g]	$C_{27}H_{29}N_5O_{10}$	C	55.6	55.6
							H	5.0	5.3
							N	12.0	12.2
III*j*	$C_6H_5OCH_2$	$OCH_2CH_2N(C_2H_5)_2$	H	40	86–87° [h]	$C_{21}H_{26}N_2O_4$	C	68.1	68.1
							H	7.1	7.0
							N	7.5	7.3
III*k*	$C_6H_5OCH_2$	$OCH_2CH_2N(C_2H_5)_2$ picrate	H	82	146–147° [g]	$C_{27}H_{29}N_5O_{11}$	C	54.1	54.1
							H	4.9	5.0
							N	11.7	11.8
III*l*	$C_6H_5OCH_2$	$OCH_2CH_2N(C_2H_5)_3I$	H	40	117–118° [e]	$C_{23}H_{31}IN_2O_4$	C	52.4	52.8
							H	6.1	5.7
							N	5.3	5.5
III*m*	1-Naphthyl	$OCH_2CH_2N(C_2H_5)_2$	H	55	147–148° [g]	$C_{24}H_{26}N_2O_3$	C	73.8	73.5
							H	6.7	6.5
							N	7.2	7.4
III*n*	1-Naphthyl	$OCH_2CH_2N(C_2H_5)_2$ picrate	H	80	179–180° [g]	$C_{30}H_{29}H_5O_{10}$	C	58.1	58.3
							H	4.7	4.8
							N	11.3	11.1
III*o*	1-Naphthyl	$OCH_2CH_2N(C_2H_5)_3I$	H	82	157–158° [e]	$C_{26}H_{31}IN_2O_3$	C	57.3	57.0
							H	5.5	5.1
							N	5.1	5.5
V*a*	2-ClC_6H_4	$NHCH_2CH_2N(C_2H_5)_2$	H	65	140–142° [c]	$C_{20}H_{24}ClN_3O_2$	C	64.3	64.7
							H	6.5	6.2
							Cl	9.5	10.0
							N	11.2	11.7

(*continued*)

Table II—*Continued*

Compound	R_1	R_2	Z	Yield, %	Melting Point	Formula		Analysis, % Calc.	Found
V*b*	2-ClC_6H_4	$NHCH_2CH_2N(C_2H_5)_3I$	H	75	Sub. 64° [i]	$C_{22}H_{29}ClIN_3O_2$	N	7.9	8.2
VIII*a*	2-ClC_6H_4	$N(C_2H_5)_2$	H	78	203–204° [j]	$C_{18}H_{19}ClN_2O_2$	C	65.4	65.0
							H	5.8	6.1
							Cl	10.7	10.9
							N	8.5	8.8
VIII*b*	2-ClC_6H_4	Pyrrolidino	H	72	173–175° [g]	$C_{18}H_{17}ClN_2O_2$	C	65.8	65.6
							H	5.2	5.2
							Cl	10.8	11.2
							N	8.5	8.7
VIII*c*	2-ClC_6H_4	Piperidino	H	80	210–211° [j]	$C_{19}H_{19}ClN_2O_2$	C	66.6	66.4
							H	5.6	5.4
							Cl	10.4	10.8
							N	8.2	8.6
VIII*d*	2-ClC_6H_4	Morpholino	H	70	167–168° [j]	$C_{18}H_{17}ClN_2O_3$	C	62.7	63.1
							H	5.0	5.4
							Cl	10.3	10.1
VIII*e*	2-ClC_6H_4	*N*-Methylpiperazino	H	75	130–131° [j]	$C_{19}H_{20}ClN_3O_2$	C	63.8	63.6
							H	5.6	5.8
							Cl	9.9	9.9
VIII*f*	3-ClC_6H_4	$N(C_2H_5)_2$	H	72	217–219° [j]	$C_{18}H_{17}ClN_2O_2$	C	65.4	65.5
							H	5.8	5.4
							Cl	10.7	11.0
							N	8.5	8.2
VIII*g*	3-ClC_6H_4	Piperidino	H	75	186–187° [j]	$C_{19}H_{19}ClN_2O_2$	C	66.6	67.0
							H	5.6	6.0
							Cl	10.3	9.9
							N	8.2	7.8
VIII*h*	3-ClC_6H_4	Morpholino	H	80	179–181° [g]	$C_{18}H_{17}ClN_2O_3$	C	62.7	63.0
							H	5.0	5.0
							Cl	10.3	10.8
							N	8.1	8.0
VIII*i*	3-ClC_6H_4	*N*-Methylpiperazino	H	65	132–133° [h]	$C_{19}H_{20}ClN_3O_2$	C	63.8	63.4
							H	5.6	5.6
							Cl	9.9	10.0
							N	11.7	11.3
VIII*j*	3-ClC_6H_4	*N*-Methylpiperazinoethiodide	H	65	201–202° [i]	$C_{21}H_{25}ClIN_3O_2$	Cl	6.9	7.2
VIII*k*	4-ClC_6H_4	Pyrrolidino	H	78	178–179° [g]	$C_{18}H_{17}ClN_2O_2$	C	65.8	65.7
							H	5.2	4.8
							Cl	10.8	11.3
							N	8.5	8.3
VIII*l*	4-ClC_6H_4	Piperidino	H	82	187–188° [g]	$C_{19}H_{19}ClN_2O_2$	C	66.6	66.5
							H	5.6	6.0
							Cl	10.4	10.7
							N	8.2	7.8
VIII*m*	4-ClC_6H_4	Morpholino	H	76	207–208° [g]	$C_{18}H_{17}ClN_2O_3$	C	62.7	62.4
							H	5.0	5.4
							Cl	10.3	9.8
							N	8.1	8.5
VIII*n*	$C_6H_5OCH_2$	Morpholino	H	56	177–178° [g]	$C_{19}H_{20}N_2O_4$	C	67.1	66.9
							H	5.9	6.1
							N	8.2	7.9
VIII*o*	$C_6H_5OCH_2$	*N*-Methylpiperazino	H	25	196–197° [k]	$C_{20}H_{23}N_3O_3$	C	68.0	68.2
							H	6.6	6.6
							N	11.9	11.7
VIII*p*	1-Naphthyl	Piperidino	H	77	195–196° [c]	$C_{23}H_{22}N_2O_2$	C	77.1	76.9
							H	6.2	6.3
							N	7.8	7.6
VIII*q*	1-Naphthyl	Morpholino	H	66	185–186° [g]	$C_{22}H_{20}N_2O_3$	C	73.3	73.2
							H	5.6	5.6
							N	7.8	8.1
VIII*r*	1-Naphthyl	*N*-Methylpiperazino	H	35	205–206° [h]	$C_{23}H_{23}N_3O_2$	C	74.0	73.6
							H	6.2	6.2
							N	11.3	10.8
IX*a*	C_6H_5	NHC_3H_7	OH	85	168–169° [j]	$C_{17}H_{18}N_2O_3$	C	68.4	68.3
							H	6.1	6.2
							N	9.4	9.0
IX*b*	C_6H_5	NHC_4H_9	OH	80	196–198° [j]	$C_{18}H_{20}N_2O_3$	C	69.2	68.8
							H	6.5	6.7
							N	9.0	8.6
IX*c*	C_6H_5	Piperidino	OH	72	190–192° [g]	$C_{19}H_{20}N_2O_3$	C	70.4	70.1
							H	6.2	5.8
							N	8.6	8.5
IX*d*	C_6H_5	Morpholino	OH	40	224–225° [h]	$C_{18}H_{18}N_2O_4$	C	66.2	66.4
							H	5.6	5.7
							N	8.6	8.8
IX*e*	C_6H_5	*N*-Methylpiperazino	OH	58	237–238° [h]	$C_{19}H_{21}N_3O_3$	C	67.2	66.7
							H	6.2	6.0
							N	12.4	12.4

[a] Known compound (II). [b] Recrystallized from methanol–ether. [c] Recrystallized from benzene. [d] Recrystallized from methanol–acetone. [e] Recrystallized from methanol–benzene. [f] Recrystallized from methanol. [g] Recrystallized from ethanol. [h] Recrystallized from benzene–petroleum ether (bp 40–60°). [i] Recrystallized from ethyl acetate. [j] Recrystallized from dilute ethanol. [k] Recrystallized from ethyl acetate–petroleum ether (bp 40–60°).

Table III—Smooth Muscle Relaxant Activity of Some of the Tested Compounds Compared to Procaine Hydrochloride

Compound[a]	Mean Reduction[b] Response[c], % ± *SE*
Procaine hydrochloride	6.5 ± 1.18
IIIc	60.0 ± 1.30
IIIe	30.3 ± 1.36
IIIg	24.0 ± 1.41
Va	48.6 ± 1.21
Vg	99.6 ± 1.50
IXc	94.0 ± 1.17

[a] The concentration used was 3×10^{-5} mole/ml. Aqueous solutions were used. [b] Average of three experiments. [c] Concentration produced by acetylcholine (0.2 μg/ml).

EXPERIMENTAL[1]

General Method (4) for Preparation of Substituted Acyl-4-aminobenzoic Acids (Ia–Id)—To a solution of 4-aminobenzoic acid (5.5 g, 0.04 mole) in 25% NaOH (100 ml) was added, with stirring, the appropriate acid chloride (Ia–Id) (0.04 mole). The mixture was shaken vigorously for 15 min, cooled, and acidified with hydrochloric acid. The crude product thus obtained was filtered, washed with water, and recrystallized from the proper solvent.

IR spectra of these acids showed peaks at 3300 (NH), 2700–2540 (OH), 1705 (aromatic COOH), and 1680, 1530, and 1260 (amide I, II, and III bands, respectively) cm^{-1}; mass spectrometry of Ia: *m/e* (relative intensity) 275 (M^+, 96), 276 ($M^+ + 1$, 31), 258 (M − OH, 9), 200 (13), 144 (16), 142 (20), 141 (98), 140 (56), 139 ($C_7H_4ClO^+$, 100), 127 (33), 113 (44), 111 ($C_6H_4Cl^+$, 84), 100 (18), 76 ($C_6H_4^+$, 13), and 75 (44).

***N*-(Diethylaminoethyl)-4-substituted Aminobenzoates (IIIa–IIIo)**—*Method A (4)*—To a cold aqueous solution of procaine hydrochloride (II) (0.01 mole) in water (50 ml) was added slowly, with stirring, the appropriate Ia–Id (0.01 mole). The mixture was rendered alkaline with sodium carbonate, and stirring and cooling were continued for 30 min. The semisolid product obtained was extracted with ether, dried, filtered, and recrystallized from the proper solvent or converted to the hydrochloride salt by passing dry hydrogen chloride through the ethereal solution.

Method B—A mixture of II (0.01 mole), the appropriate Ia–Id (0.01 mole), and sodium bicarbonate (0.02 mole) in dry benzene (50 ml) was refluxed for 1–2 hr and filtered. The product was recrystallized from the proper solvent.

Method C (5–8)—A solution of II (0.01 mole) in water (10 ml) was made alkaline with ammonium hydroxide solution, and the liberated procaine base was extracted with chloroform. To the dry chloroform solution, *N,N'*-dicyclohexylcarbodiimide (0.01 mole) and the appropriate acid (0.01 mole) were added with cooling to 0° for 1 hr. Then the reaction mixture was left at room temperature overnight and filtered from the precipitated dicyclohexylurea. The filtrate was concentrated under reduced pressure, and the product was converted to the picrate salt.

***N*-(Diethylaminoethyl)-4-substituted Aminobenzamides (Va and Vb): Method D (9, 10)**—To a cooled, stirred solution of procainamide hydrochloride (IV) (0.005 mole) in dry pyridine (5 ml) was gradually added a cold solution of the appropriate Ia–Id (0.005 mole) in dry pyridine (5 ml) over 15 min. Stirring and cooling were continued for 1 hr, pyridine was removed under reduced pressure, and the residue was treated with ice cold water. The white precipitate thus obtained was collected, washed with water, and recrystallized from the proper solvent.

The IR spectra of Va showed a peak at 3340–3250 cm^{-1} indicative of NH (a secondary amide) and an amide I band at 1680 cm^{-1}. The PMR spectrum of Va ($CDCl_3$) exhibited peaks at δ 0.81–0.96 (t, 6H, $2CH_3$), 2.2–2.5 [q, 6H, $CH_2N(CH_2)_2$], 3.2 (q, 2H, C-2 of ethylenediamine), 6.2 (b, 1H, NH), and 7.0–7.5 (m, 8H, aromatic) ppm.

Quaternary Salts—To a solution of the amino compound (0.01 mole) in dry ether (50 ml) was added ethyl iodide (0.011 mole), and the mixture was stirred at room temperature for 24 hr. Ether was evaporated, and the product was recrystallized from the proper solvent.

4-Substituted Acylaminobenzamides (VIIIa–VIIIr)—These compounds were prepared following Methods B and D. Their IR spectra showed a peak at 3340–3250 cm^{-1} indicative of NH (a secondary amide) and an amide I band at 1680 cm^{-1}.

Mass spectrometry of VIIIe indicated *m/e* (relative intensity) 357 (M^+, 5), 258 ($M^+ - C_5H_{11}N_2^+$, 5), 218 ($C_{12}H_{16}N_3O^+$, 3), 141 (45), 140 (C_7H_5ClO, 14), 139 ($C_7H_4ClO^+$, 100), 113 (12), 111 ($C_6H_4Cl^+$, 38), 100 ($C_5H_{12}N_2$, 20), 99 ($C_5H_{11}N_2^+$, 6), 91 ($C_6H_5N^+$, 8), 76 ($C_6H_4^+$, 12), and 75 ($C_6H_3^+$, 22). The PMR spectrum of VIIIe (dimethyl sulfoxide-d_6) exhibited peaks at δ 2.25 (s, 3H, CH_3N-4), 2.33–2.4 (d, 4H, C_3 and C_5 piperazine), 3.45–3.6 (t, 4H, C_2 and C_6 piperazine), 7.33–7.9 (m, 8H, aromatic), and 10.67 (s, 1H, NH) ppm.

The PMR spectrum of VIIIb ($CDCl_3$) exhibited peaks at δ 1.88 (m, 4H, C_3 and C_4 pyrrolidine), 3.45–3.5 (d, 4H, C_2 and C_5 pyrrolidine), and 7.37–8.16 (m, 8H, aromatic) ppm.

The PMR spectrum of VIIIg ($CDCl_3$) exhibited peaks at δ 1.29–1.65 (t, 6H, C_3 and C_4 piperidine), 3.55 (s, 4H, C_2 and C_6 piperidine), 7.25–8.06 (t, 7H, aromatic), and 9.4 (s, 1H, C_2 of 3-chlorobenzoyl) ppm.

The PMR spectrum of VIIIi ($CDCl_3$) exhibited peaks at δ 2.3 (s, 3H, CH_3N-4), 2.36–2.38 (d, 4H, C_3 and C_5 piperazine), 3.59 (b, s, 4H, C_2 and C_6 piperazine), 7.26–7.94 (m, 7H, aromatic), and 8.57 (s, 1H, C_2 of 3-chlorobenzoyl) ppm.

4-Substituted Acylaminosalicylamides (IXa–IXe)—These compounds were prepared following Method B.

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[1] IR spectra were determined on a Beckman IR-4210 as Nujol mulls. PMR spectra were determined on a Perkin-Elmer R12 spectrometer with tetramethylsilane as the internal standard. Mass spectra were determined using an AEI MS9 spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.