

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NEW
2,4,-(1H, 3H) QUINAZOLINEDIONE DERIVATIVES.

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ABSTRACT

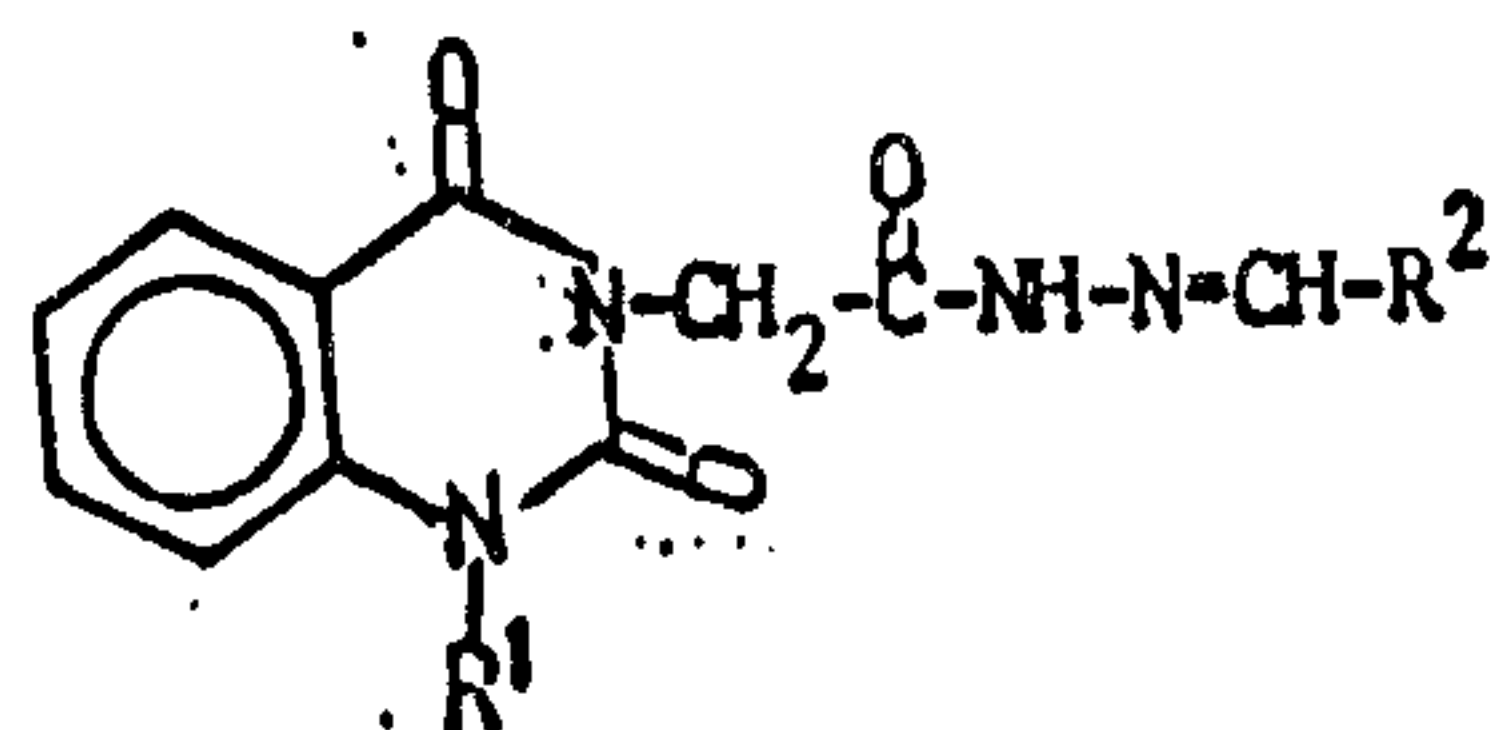
Some new (1H, 3H) quinazolinedione derivatives were prepared, their structures were confirmed by microanalysis and IR. Some of them were confirmed by NMR and mass spectra, some of these compounds are active as anticonvulsants.

INTRODUCTION

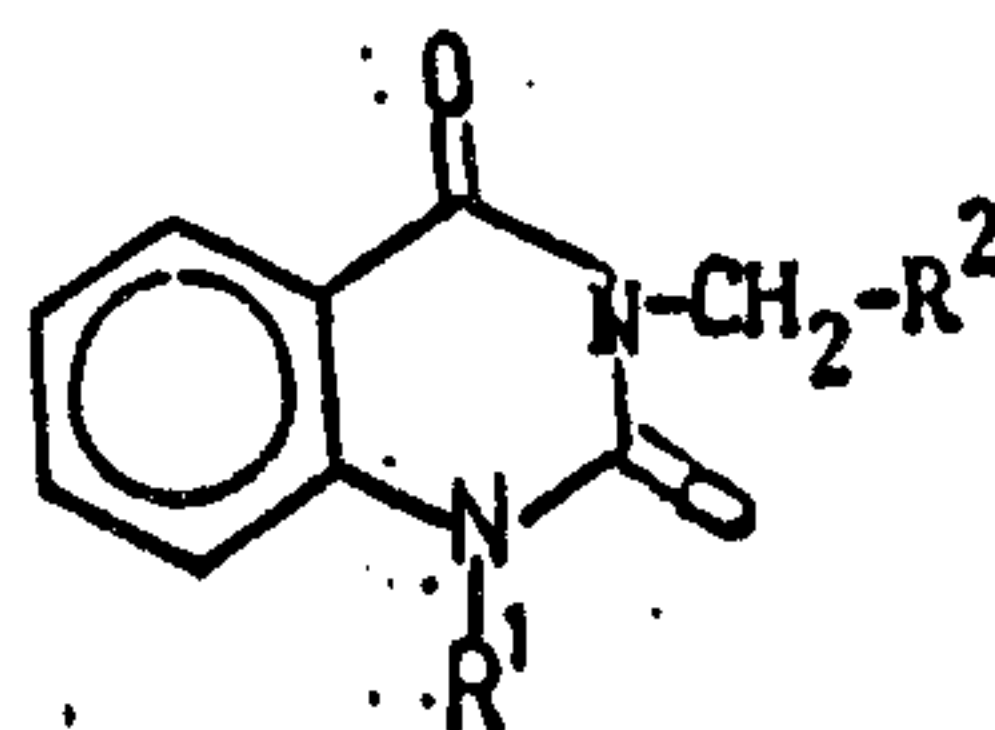
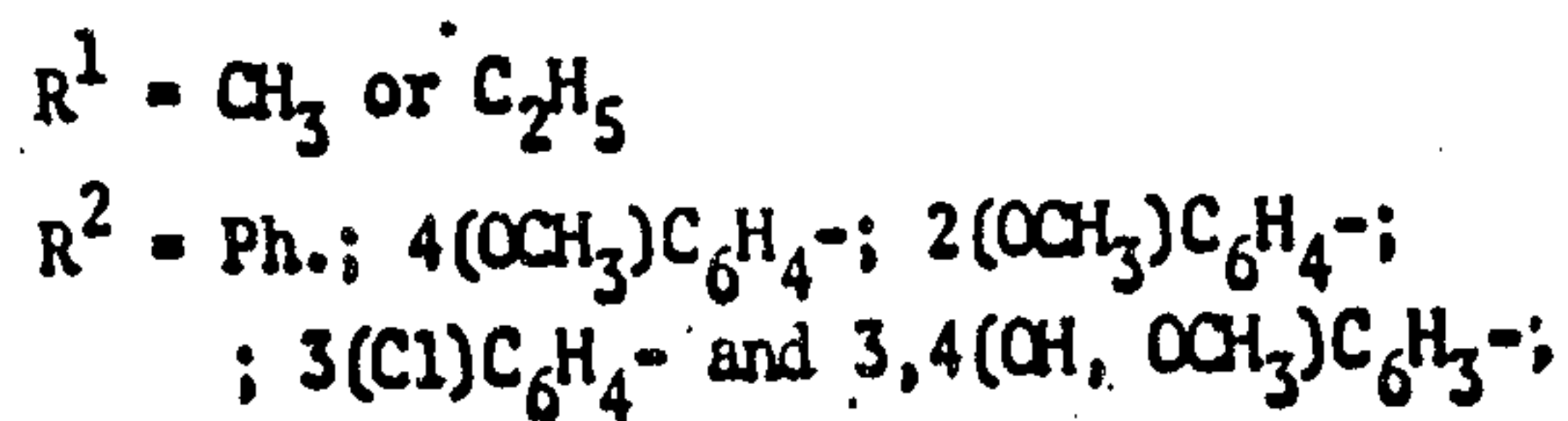
Investigation over the last twenty years has demonstrated that quinazoline nucleus is capable of exhibiting a wide variety of pharmacological activities e.g. CNS depressant, diuretic, antihypertensive, antiinflammatory, analgesic and other diverse activities¹.

In addition, it is well known that some 2,4-(1H,3H) quinazolindiones possess anticonvulsant and hypnotic activities². Moreover, 2-alkyl-3-aryl-4(3H)-quinazolones possess an anticonvulsant activity^{3,4}. Kostadinova *et al*⁵ reported later on, that 2-methyl-3-p-chlorophenyl-4(3H)quinazoline inhibits the basolateral amygdaloid-induced excitation in the optical zone of the cortex, the reticular formation and hypothalamus and exhibits an anticonvulsant action.

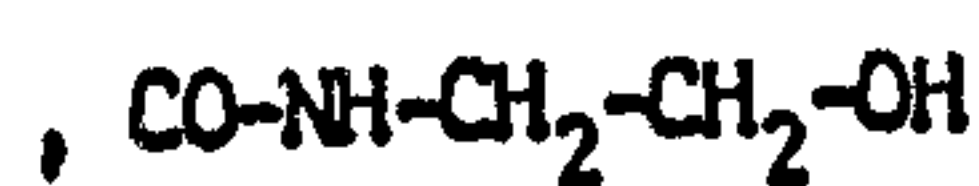
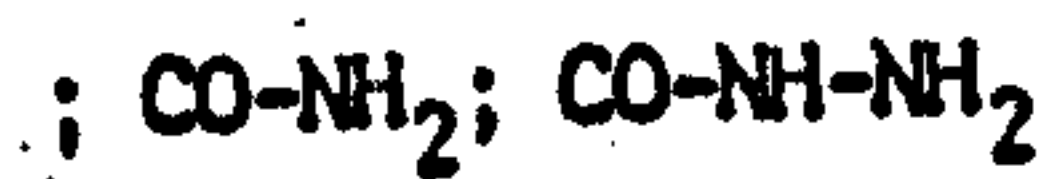
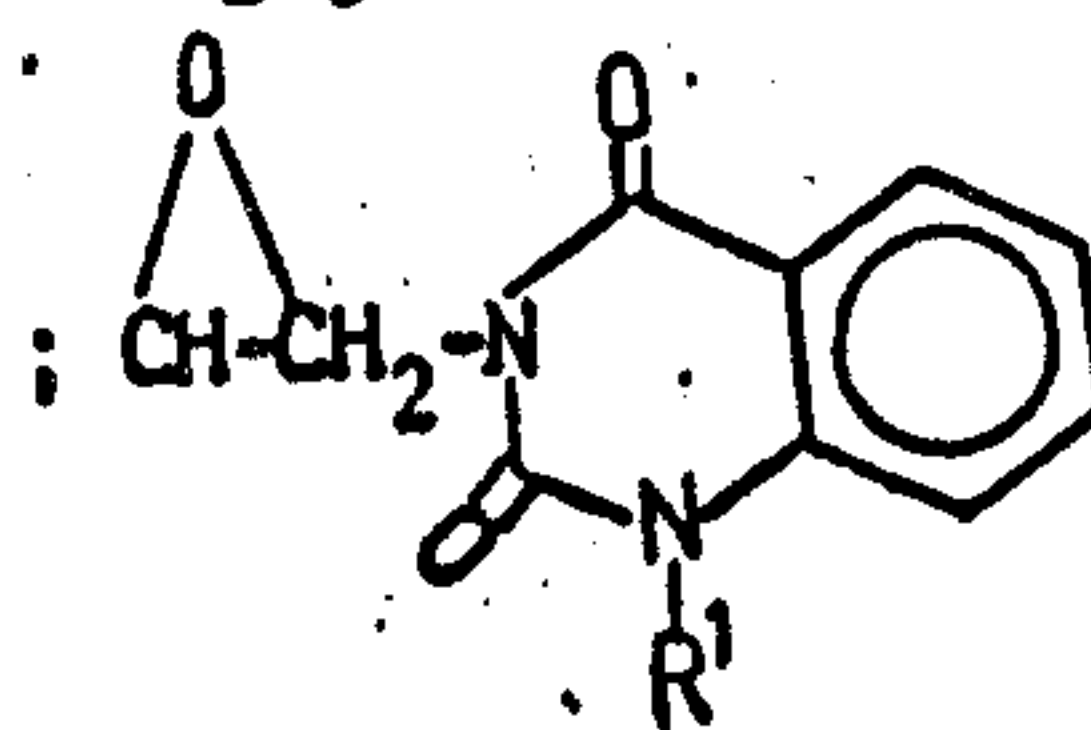
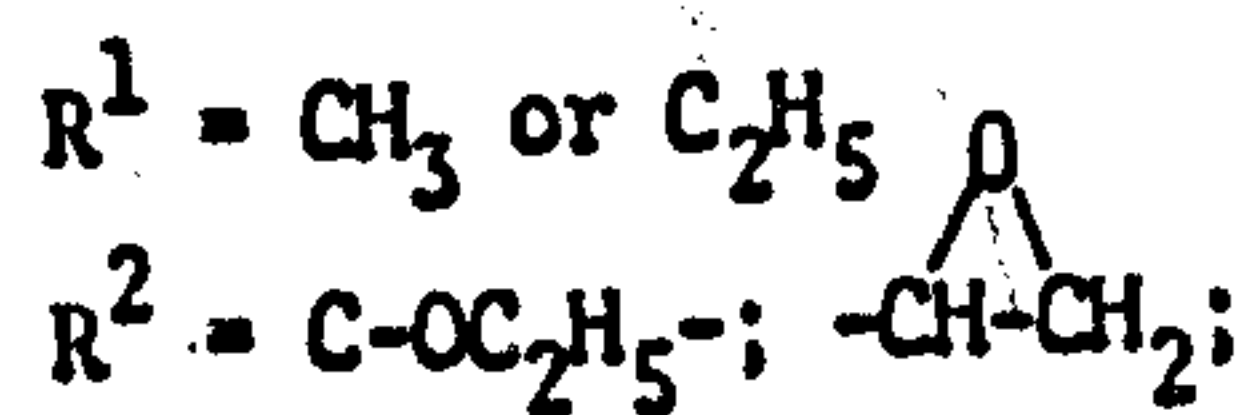
Recently, Ossman and Barakat synthesized some derivatives of 4(3H)-quinazolone which possess anticonvulsant activity⁶. So, it seemed most interesting to prepare the following series of new 2,4-(1H, 3H) quinazolinedione of the general Formula I, II.



I.

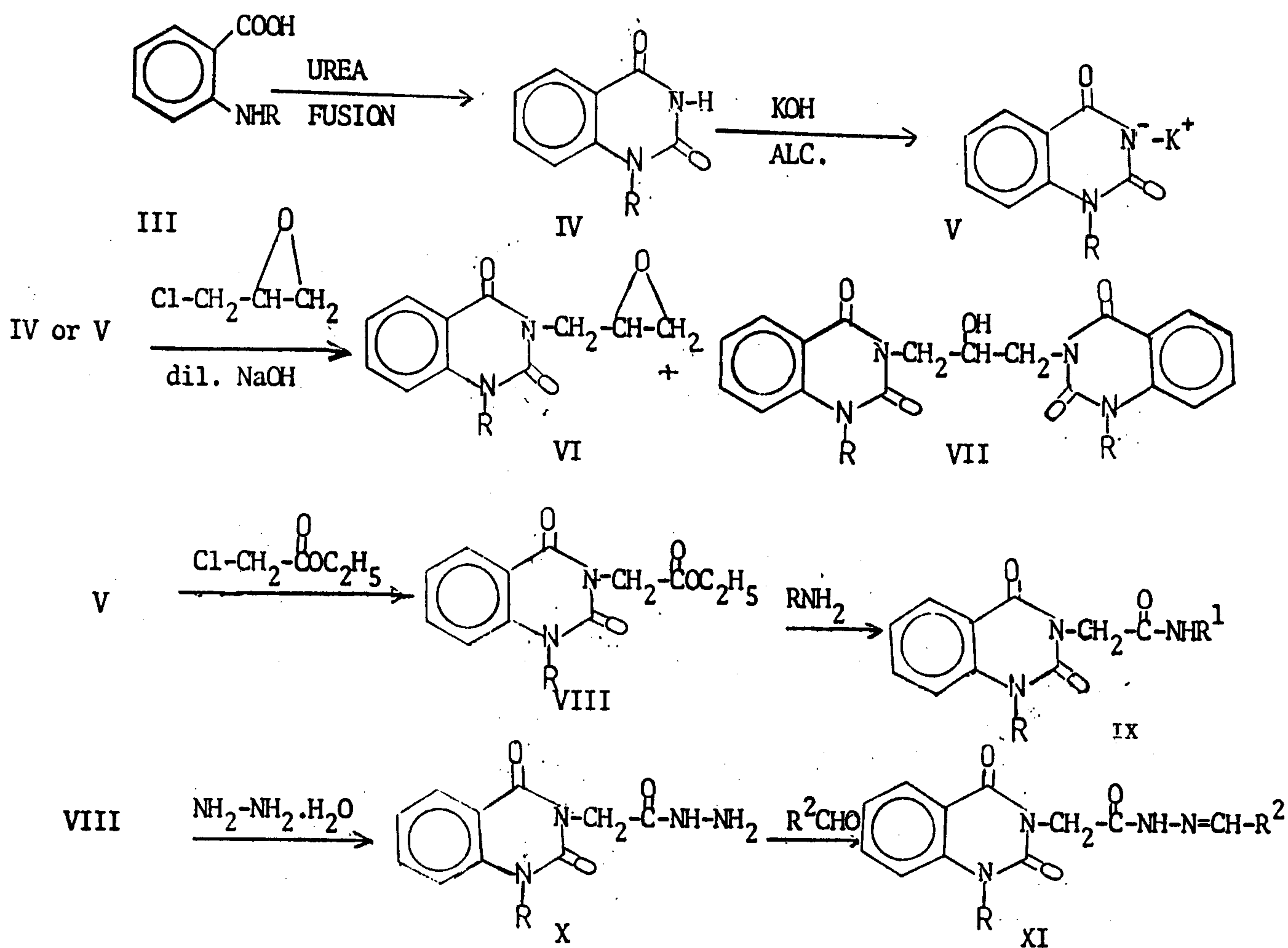


II



Synthesis and Anticonvulsant Activity of Some New 2,4-(1H,3H) Quinazolinedione Derivatives

For the synthesis of such compounds of the general formula I,II and their intermediates, the following Scheme was proposed:



R = CH₃ or C₂H₅

R¹ = H; -NH₂; -CH₃; -CH₂-CH₂-OH; CH₂-CH₂-CH₃; C₆H₁₁; C₆H₅-CH₂-

R² = Ph; 4(OCH₃)C₆H₄-; 2(OCH₃)C₆H₄-; 3(Cl)C₆H₄-; 3,4(OH, OCH₃)C₆H₃-

EXPERIMENTAL

- 1- All melting points were carried out by open capillary method on a Galenkamp apparatus and are uncorrected.
- 2- Microanalyses were performed at the microanalytical unit of the Faculty of Science, Cairo University, Cairo, Egypt.
- 3- IR spectra were recorded on a Pye-unicam SP-1100 infrared spectrophotometer in KBr at the Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt and at the Faculty of Science, Cairo University.
- 4- NMR spectra were recorded on a Geol 90-MHz spectrometer at the department of Chemistry, University of Pittsburg, U.S.A.

Reported procedures were adopted for the synthesis of the required intermediates, namely N-ethyl and N-methyl anthranilic acid⁷, 1-ethyl and 1-methyl-2,4-(1H, 3H) quinazolinedione^{8,9}.

The following are the methods for the preparation of the new compounds:

1- Preparation of potassium salts (V) of 1-alkyl-2,4- (1H, 3H) quinazoline-dione.

Solution of potassium hydroxide (0.01 mole in 5 ml absolute ethanol) was added to solution of compounds IV (0.01 mole in 5 ml absolute ethanol). The salts separated were filtered off, washed with absolute ethanol and dried in vacuum.

2- Preparation of esters (VIII) (1-alkyl-3-carbethoxy methyl 2,4- (1H, 3H) quinazolinedione)

Potassium salts V (0.01 mole) and ethyl chloroacetate (0.0 mole) were refluxed in DMF (5 ml) on a water bath for two hours. The reaction mixture was poured into cold water (200 ml) and the separated crude esters were filtered off, then recrystallized from ethanol.

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3- Preparation of amides, IX (General procedure).

Esters VIII (0.01 mole) and the appropriate amines (0.01 mole) were refluxed in ethanol (10 ml) for two hours and half. The reaction mixture was poured into cold water (200 ml), the crude products were filtered off, dried and then recrystallized from ethanol.

4- Preparation of azomethines, XI (General procedure).

Hydrazide X (0.0 mole) and the appropriate aldehydes (0.0 mole) were refluxed in glacial acetic acid (10 ml) for two hours and half. The reaction mixture was poured into cold water (200 ml). The crude products were filtered off, dried and then recrystallized from dioxan.

5- Preparation of compound VI (1-alkyl-3-{oxiranyl methyl}-2,4 (1H, 3H) quinazolinedione) and compound VII Bis-{1-alkyl-2,4 (1H, 3H) quinazolinedione}-prop-2-ol.

Method(A) :

Epichlorohydrin (1 ml) was added to a solution of IV (0.0 mole), sodium hydroxide (10 ml of 10% solution), the reaction mixture was shaken for 30 minutes and allowed to stand for two hours. From the solid products obtained by fractional crystallization, compounds VI and VII were isolated.

Method (B) :

It was possible to prepare compounds VI, VII starting from potassium salt V instead of compound IV by the following method: the salt V (0.01 mole) and epichlorohydrin (1 ml) were refluxed in DMF for two hours, the reaction mixture was poured into cold water (200 ml), filtered off, washed and recrystallized from ethanol.

RESULTS AND DISCUSSION

N-ethyl and N-methyl anthranilic acids, III, as well as 1-ethyl and 1-methyl-2,4-(1H, 3H)-quinazolinedione, IV, Scheme I, were prepared according to reported procedures.

The potassium salts V were prepared by the action of alcoholic potassium hydroxide on compounds IV, these salts were refluxed with ethyl chloroacetate in DMF to give two new esters No. (1,2) Table 1, the esters when allowed to react with different amines gave new different amides No. (1-11) Table 2.

The new esters when reacted with hydrazine hydrate (50 %) gave the hydrazide X Scheme I and No. (2,8) Table 2.

The hydrazides when allowed to react with different aldehydes gave new azomethines X and No. (1-6) Table 3. The structures of these compounds were confirmed by microanalysis data (Table 1,2,3), IR, NMR and mass spectra data.

IR spectra of the two esters No. (1,2) Table 1, showed characteristic frequencies, thus exhibiting 2-position carbonyl bands in the range of 1610-1680 cm^{-1} , 4-position carbonyl bands at 1710 cm^{-1} , and the ester carbonyl band at 1760 cm^{-1} , out of plane C-H bending of the adjacent protons (4 protons of the aromatic ring system) appeared at 760 cm^{-1} . Amides IX, Scheme I, showed the NH and NH_2 stretching bands at the range of 3300-3600 cm^{-1} .

Azomethines XI, Scheme I, showed C=N stretching frequency in the range 1640-1690 while the NH stretching was showed at 3230 cm^{-1} .

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(1H, 3H) Quinazolinedione Derivatives.*

Compound No. (4) (Table I) showed broad band at 3480-3510 cm^{-1} due to the OH stretching frequency. Compound No.(3) (Table 1) showed a band at 1000-1200 cm^{-1} due to the presence of an ether linkage of the epoxide structure.

Further confirmation for the structure of some compounds was obtained from NMR and mass spectra shown under Table 1.

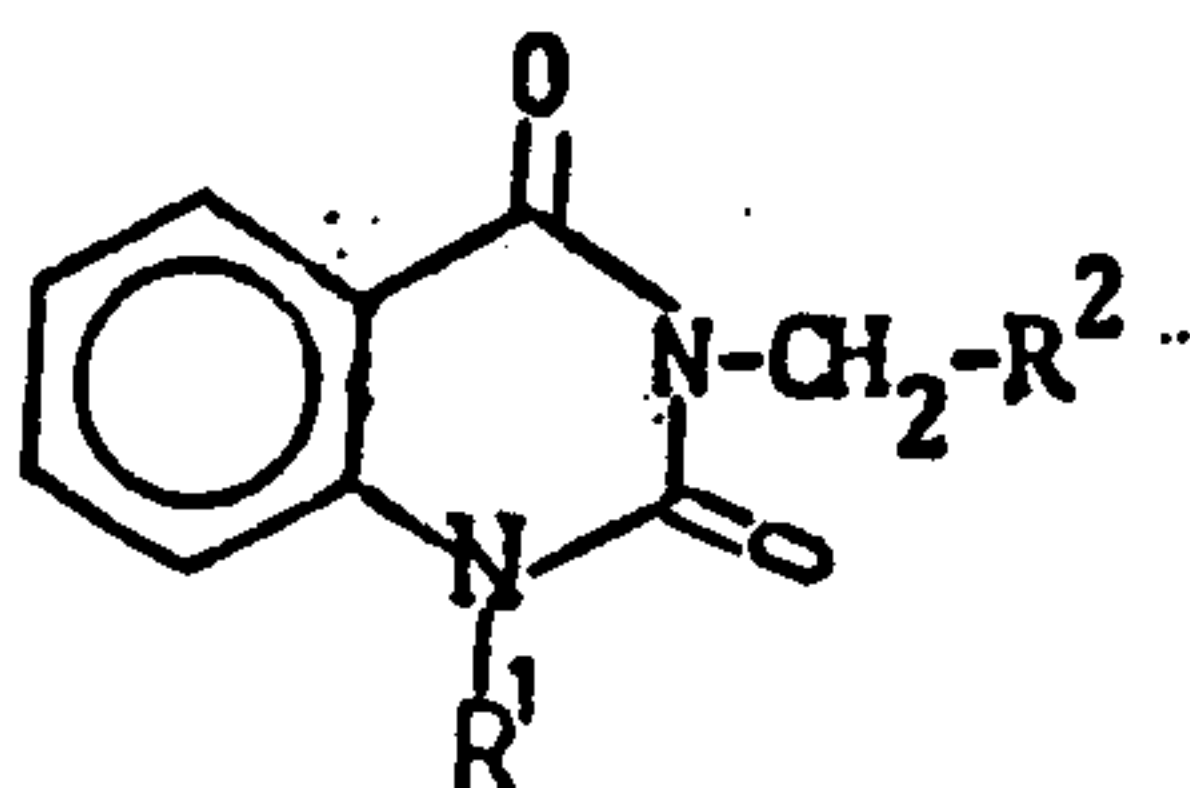
Interstingly enough, the reaction of epichlorohydrin with the potassium salt of 1-alkyl-(1H, 3H)-quinazolinedione afforded two compounds (4 and 5) (Table 1).The structure of bis {1-ethyl (1H, 3H)-quinazolindione}prop-2-ol was confirmed by Mass and NMR spectra, Scheme 1.

Pharmacological Testing:

Five compounds: 1,2 (Table 1), 9, 10 (Table 2) and 4 (Table 3) were tested for the anticonvulsant activity against pentylenetetrazol-induced convulsions in frogs following the method reported by Soaje-Echaque and Lim¹¹, using phenobarbitone sodium as a reference compound.

Compounds 1, 2 (Table 1) were the most potent of the tested compounds, while the least potent compound was compound 4 (Table 3).

Table 1.



Comp.	R1	R2	m.p °C	Yield %	Molecular Formula	Elemental Analysis	
						Calcd	Found
1	C ₂ H ₅		70	80	C ₁₄ H ₁₆ N ₂ O ₄	C% 60.86 H% 5.79 N% 10.14	60.7 5.8 10.3
2	CH ₃		119	80	C ₁₃ H ₁₄ N ₂ O ₄	C% 59.54 H% 5.34 N% 10.68	59.8 5.00 11.00
3	C ₂ H ₅		119	65	C ₁₃ H ₁₄ N ₂ O ₃	C% 63.41 H% 5.69 N% 11.38	63.2 5.9 11.7
4	C ₂ H ₅		198	80	C ₂₃ H ₂₄ N ₄ O ₅	C% 63.30 H% 5.50 N% 12.84	63.30 5.60 12.6
5	CH ₃		230	90	C ₂₁ H ₂₀ N ₄ O ₅	C% 61.76 H% 4.90 N% 13.72	61.8 4.8 13.8

* PMR(DMSO): δ 1.2(6H, t), 4.2(4H, q), 2.4(2H, s) 7.2-8.5(4H, m) Ar-H.

** PMR(DMSO): δ 1.2(3H, t), 4.2(2H, q), 2.0(3H, s) 7.2-8.5(4H, m) Ar-H.

+ PMR(DMSO): δ 1.2(3H, t), 4.1(2H, q), 2.5(5H, pentet), 7.2-8.1(4H, m) Ar-H.

++ PMR(DMSO): δ 1.2(6H, t), 4.0(4H, q), 4.8(1H, m), 7.2-8.1(8H, m) Ar-H.

Mass spectra data

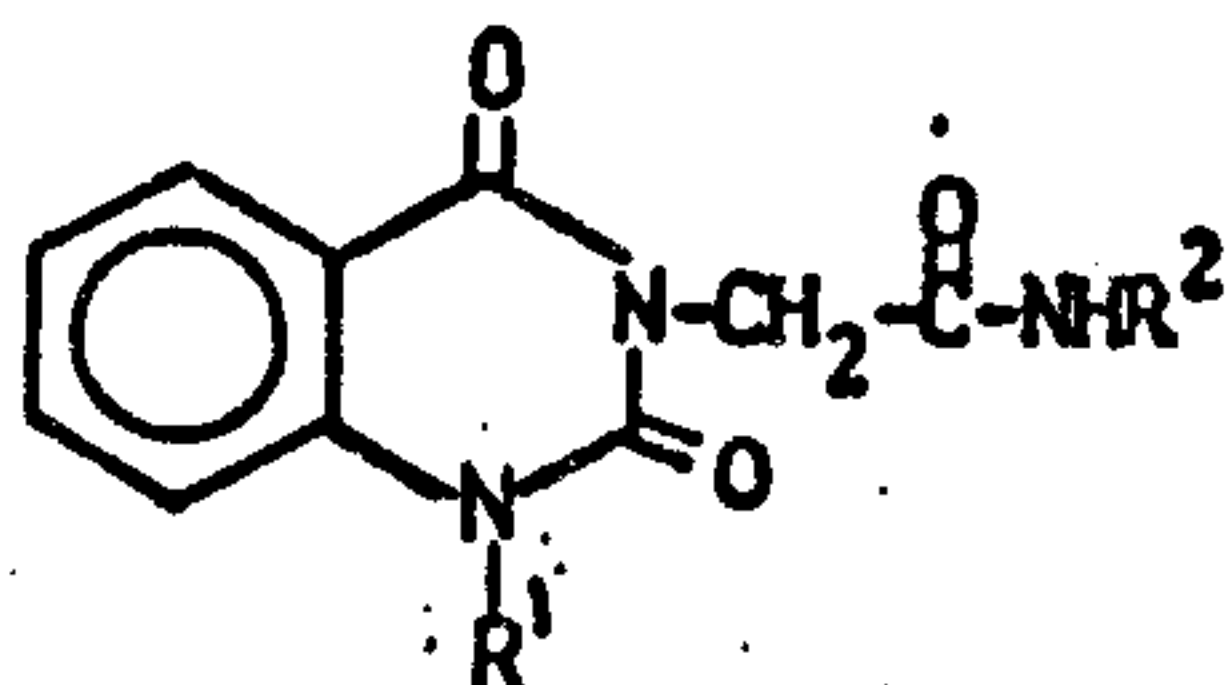
* 276 M⁽⁺⁾ (100%) Base peak, m/e 232(13.07%), m/e 204/205 (12.46%), m/e 118/119 (8%), m/e 90(8.87%).

** m/e 262(51.69%), m/e 218(7.94%), 190 M⁽⁺⁾ (100%), Base peak, 105/104(13.93%), m/e 89/88 (11.76%).

+ M⁽⁺⁾ 246 (100%) Base peak, m/e 203/202 (12.08%), m/e 174/175 (4.45%), m/e 145/146 (4.54%), m/e 119 (6.21%), m/e 90(5.15%).

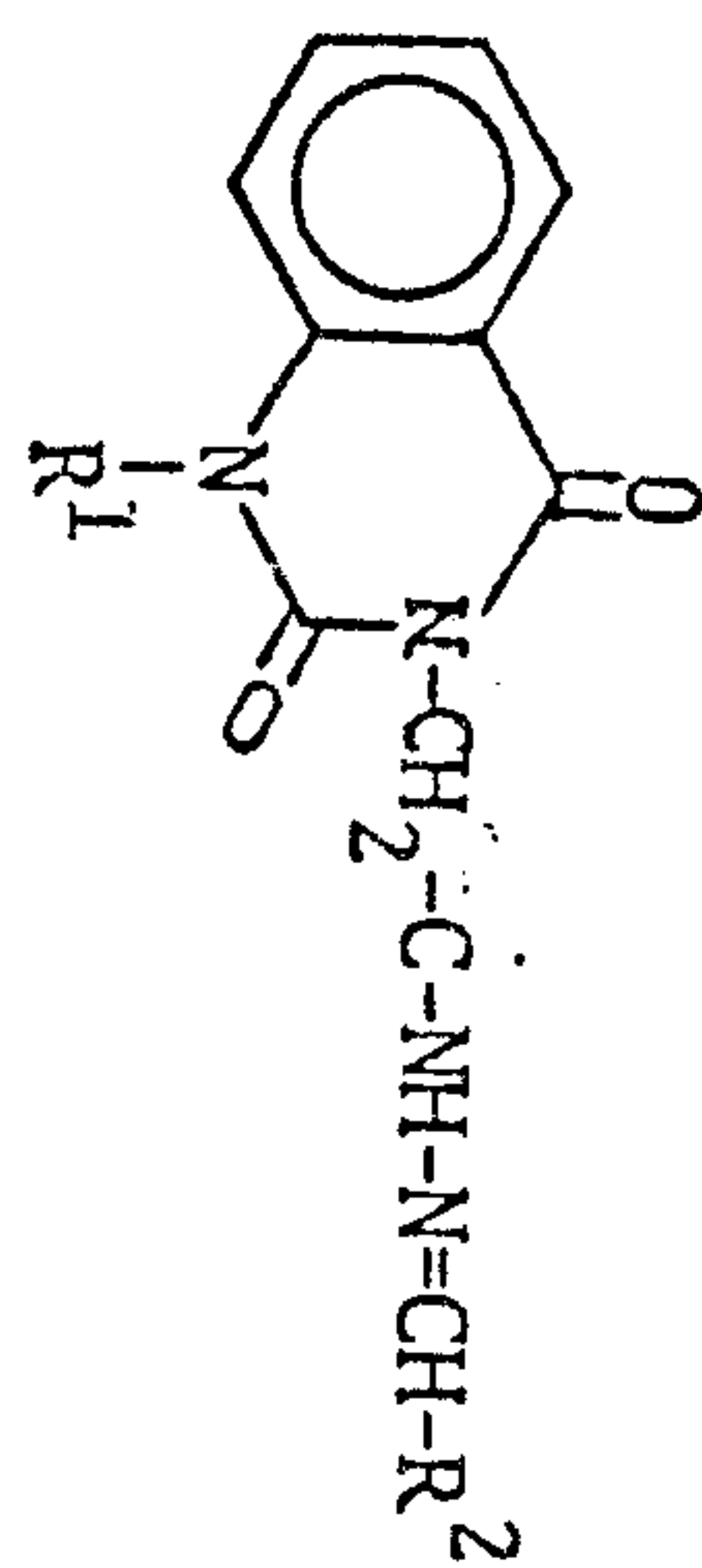
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Table 2.



Comp.	R	R1	m.p °C	Yield %	Molecular Formula	Elemental Analysis	
						Calcd	Found
1	C ₂ H ₅	H	234	100	C ₁₂ H ₁₃ N ₃ O ₃	C% 58.29 H% 5.26 N% 17.00	58.7 5.00 17.20
2	C ₂ H ₅	-NH ₂	215	100	C ₁₂ H ₁₄ N ₄ O ₃	C% 54.96 H% 5.34 N% 21.37	55.2 5.10 21.8
3	C ₂ H ₅	-CH ₃	249	95	C ₁₃ H ₁₄ N ₃ O ₃	C% 59.77 H% 5.74 N% 16.09	59.8 5.7 16.4
4	C ₂ H ₅	-CH ₂ -CH-OH	(190-2)	95	C ₁₄ H ₁₇ N ₃ O ₄	C% 57.73 H% 5.84 N% 14.43	57.30 5.90 14.70
5	C ₂ H ₅	-CH ₂ -CH ₂ -CH ₃	174	80	C ₁₅ H ₁₉ N ₃ O ₃	C% 62.28 H% 6.57 N% 14.53	62.3 6.3 14.4
6	C ₂ H ₅	-C ₆ H ₁₁	193	100	C ₁₈ H ₂₃ N ₃ O ₃	C% 65.65 H% 6.99 N% 12.76	65.4 6.7 13.1
7	C ₂ H ₅	-CH ₂ -C ₆ H ₅	185-6.	100	C ₁₉ H ₁₉ N ₃ O ₃	C% 67.65 H% 5.63 N% 12.46	67.4 5.5 12.1
8	CH ₃	-NH ₂	265	90	C ₁₁ H ₁₂ N ₄ O ₃	C% 53.22 H% 4.83 N% 22.58	53.50 4.80 22.9
9	CH ₃	-CH ₃	288	100	C ₁₂ H ₁₃ N ₃ O ₃	C% 58.29 H% 5.26 N% 17.00	58.3 5.5 17.4
10	CH ₃	-CH ₂ -C ₆ H ₅	240	80	C ₁₈ H ₁₇ N ₃ O ₃	C% 66.87 H% 5.26 N% 13.00	66.6 5.3 13.00
11	CH ₃	CH ₂ -CH ₂ -OH	240	100	C ₁₃ H ₁₅ N ₃ O ₄	C% 57.99 H% 5.57 N% 15.61	58.2 5.6 15.1

Table 3.



Comp.	R1	R2	m.p °C	Yield %	Molecular Formula	Elemental Analysis	
						Calcd	Found
1	C ₂ H ₅	C ₆ H ₅	238-40	90	C ₁₉ H ₁₈ N ₄ O ₃	C% 65.14 H% 5.14 N% 16.00	64.8 5.4 15.6
2	C ₂ H ₅	-C ₆ H ₄ (4-MeO)	(254-6)	97	C ₂₀ H ₂₀ N ₄ O ₄	C% 63.15 H% 5.26 N% 14.73	63.2 5.2 14.3
3	C ₂ H ₅	-C ₆ H ₄ (2-MeO)	(270-2)	95	C ₂₀ H ₂₀ N ₄ O ₄	C% 63.15 H% 5.26 N% 14.73	63.00 5.2 14.4
4	C ₂ H ₅	-C ₆ H ₄ (3-Cl)	(265-6)	100	C ₁₉ H ₁₇ N ₄ O ₃ Cl	C% 59.37 H% 4.42 N% 14.58	59.3 4.2 14.7
5	C ₂ H ₅	C ₆ H ₃ (3-OH,4-MeO)	326 (decomp.)	70	C ₂₀ H ₂₀ N ₄ O ₅	C% 60.60 H% 5.05 N% 14.14	60.1 5.0 14.5
6	CH ₃	C ₆ H ₄ (2-MeO)	265	70	C ₁₉ H ₁₈ N ₄ O ₄	C% 62.29 H% 4.9 N% 15.30	62.8 5.0 15.7

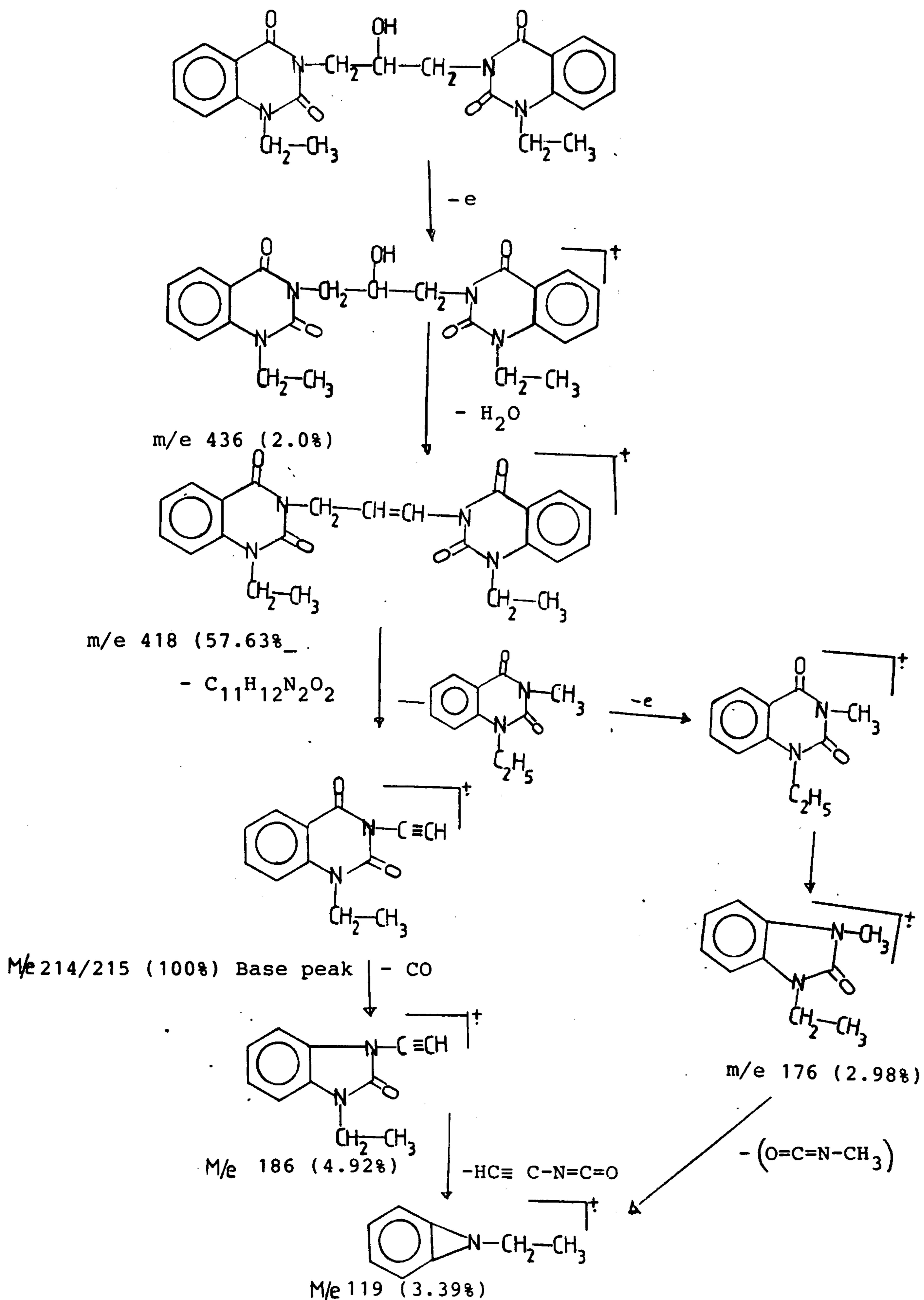
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Table 4.: Effect of phenobarbitone and test compounds on pentylenetetrazol-induced convulsions in frogs.

Comp.	Dose mg/kg	No. of frogs injected	No. of frogs protected	Protection %	Protective D ₅₀	Relative potency to phenobarbitone
1	200	10	10	100	110	0.82
	100	10	7	70		
	50	10	2	20		
2	200	10	10	100	100	0.90
	100	10	5	50		
Table 1	50	10	2	20		
9	800	10	8	80	560	0.17
Table 2	400	10	3	30		
10	800	10	7	70	580	0.16
Table 2	400	10	2	20		
4	800	10	6	60	700	0.13
Table 3	400	10	2	20		
P*	200	10	10	100	90	1.00
	150	8	6	75		
	100	10	6	60		
	50	10	3	30		

* P : Phenobarbitone

Scheme 1: Fragment. Pattern of Bis[(1-ethyl-2,4 (1H, 3H)-dioxo quinazoliny] prop-2-ol].



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تخليق بعض مشتقات ٢ ، ٤ (ايد ، ٣ يد) كينازولين دايون الجديدة
بهدف دراستها اقربازينيا كمضادات للتشنجات العصبية

عبد الرحمن الناصر عثمان - عبد الغنى على الهلبى - عبد الجابر نصر عثمان*
قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة الأزهر
قسم الكيمياء العضوية - كلية الصيدلة - جامعة القاهرة*

فى هذ البحث امكن تخليق بعض المركبات الجديدة المشتقة من نواة ١ - اثيل
أو ١ - ميثيل ٢ ، ٤ (ايد ، ٣ يد) كينازولين دايون وذلك بتحضير ملح
البوتاسيوم منها ثم تكثيفه مع خلات كلورو الايثيل ثم بتفاعل الاسترات الناتجة
مع مجموعة من الامينات فتعطى مجموعة من الاميدات وبتفاعلها مع الهيدرازين
تعطى الهيدرازيدات ثم بتكثيف الاخيرة مع مجموعة من الالدهيدات تعطى مركبات
جديدة من الازومثيين .

وقد امكن تفاعل هذا الملح البوتاسيومى مع الابى كلوروهيدرين ونتج ايضا
عدد من المركبات الجديدة .

وقد امكن اختبار خمسة من هذه المركبات وعددهم (٢٢) فثبت ان لهم
فاعلية فى علاج التشنجات العصبية ووجد ان احدهما يعادل ٩٠ ٪ والاخر ٨٢ ٪
من فاعلية مادة الفينوباربيتون صوديوم ، المستخدم فى علاج التشنجات العصبية
وتم التعرف على صيغتها البنائية باستعمال الرنين النووى المغناطيسى
والاشعة دون الحمراء والتحليل الدقيق .

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