

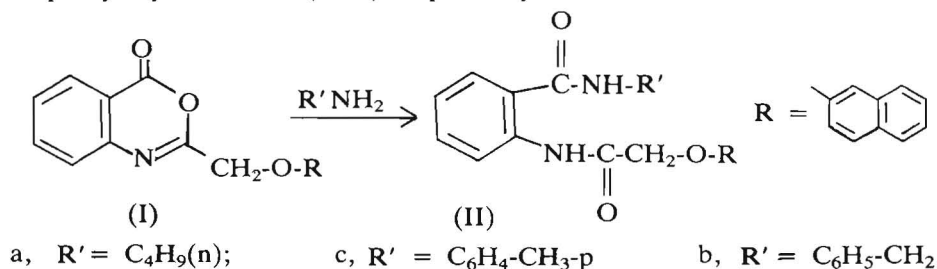
Some Reactions of 2-(2'-Naphthyloxymethyl)- 4H-3,1-Benzoxazine-4-One

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ABSTRACT. The benzoxazinone (I) reacted with primary amines and yielded the carbamoylacetyl derivatives (IIa-c), but aniline in boiling benzene/phosphorus oxychloride gave the quinazolinone (III). (I) reacted with secondary amines and gave the carbonyl acetanilide derivative (IV). Hydrazinolysis of (I) gave the quinazolinone (Va & b). Compound (Va) condensed with aromatic aldehydes and reacted with phosphorus pentasulphide to give (VIa-d) and (VII) respectively. The reaction of active methylene compounds with (I) gave (VIII) or (IX) respectively. Also (I) reacted with formamide to yield (X) and with sodium azide in boiling acetic acid to give (XI) and (XII) respectively.

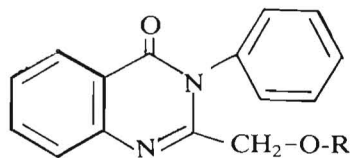
The present investigation deals with the reaction of 2-(2'-naphthyloxy-methyl)-4H-3,1-benzoxazine-4-one (I) with some nucleophilic reagents such as amines, hydrazines, carbanions, azide and formamide, see all the references listed in this paper. Similar to other 3,1-benzoxazine-4-ones, (I) underwent ring opening reaction with primary amines (Sammour *et al.* 1971 and Essawy *et al.* 1982) namely, n-butylamine, benzylamine or p-toluidine in boiling ethanol or benzene to give the corresponding 2-(n-butyl, benzyl or p-tolyl)carbamoyl-2'naphthyloxyacetanilide (IIa-c) respectively.



The structure of compounds (II) was confirmed by: i) IR spectra showing ν_{\max} 1690-1660 (C=O) and 3330-3250 cm^{-1} (NH). ii) PMR spectrum of compound (IIa) showed signals (δ) at 0.9 (t, 3H, $\text{CH}_3\text{-(CH}_2\text{)}_3\text{-}$), 1.4 (m, 4H, $\text{-(CH}_2\text{)}_2\text{-}$), 2.8 (t,

2H, $\text{HN-CH}_2\text{-CH}_2\text{-}$), 4.8 (s, $\text{2H-C(=O)-CH}_2\text{-O-}$) and at 7.3 - 8.2 (m, 11H, aromatic protons).

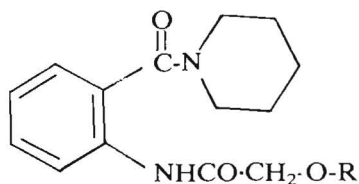
However, aniline reacted with (I) in boiling benzene/phosphorus oxychloride to give (2-(2'-naphthyloxymethyl)3-phenyl-4(3H)-quinazolinone (III).



(III)

The structure of compound (III) was confirmed by IR spectrum showing ν_{\max} 1680 (CO) and the absence of the band in the region 3330-3200 cm^{-1} due to ν_{\max} (NH).

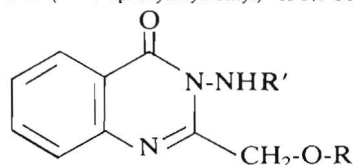
On the other hand, the secondary amine piperidine reacted with compound (I) in boiling benzene and yielded 2-piperidino carbonyl-2'-naphthyloxacetanilide (IV)



(IV)

The structure of (IV) was supported by: i) IR spectrum showing ν_{\max} 1670 (CO) and 3260 cm^{-1} (NH). ii) PMR spectrum showed signals (δ) at 4.8 (s, 2H, $\text{-CO-CH}_2\text{-O-}$), 2.74 (t, 4H, $\text{-CH}_2\text{-N-CH}_2\text{-}$), 1.5 (m, 6H, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-}$) and at 7.3 - 8.1 (m, 11 H, aromatic protons).

It has been found that compound (I) reacts with hydrazine (El Hashash and Sayed 1978) hydrate or phenylhydrazine to give 2-(2'-naphthyloxymethyl)-3-(amino or phenylamino)-4(3H)-quinazolinone (Va & b) respectively).

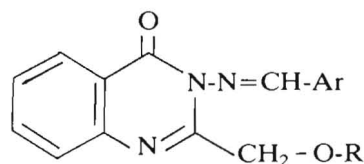


(V)

a, $R' = H$; b, $R' = -C_6H_5$

The IR spectrum of compound (V) exhibited bands ν_{\max} 1685 (CO), 1640 (C=N) and 3330 cm^{-1} (NH).

Compound (Va) condensed with aromatic aldehydes, namely p-chlorobenzaldehyde, anisaldehyde, o-nitrobenzaldehyde or p-nitrobenzaldehyde and yielded 3-(p-chloro, p-methoxy, o-nitro- or p-nitrobenzylidene amino)-2-(2'-naphthyloxymethyl)-4(3H)-quinazolinone (VIa-d) respectively.

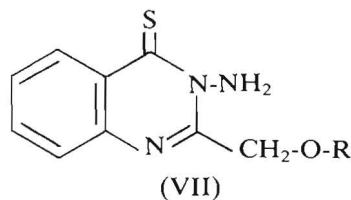


(VI)

a, $AR = C_6H_4Cl-p$; b, $Ar = C_6H_4-OCH_3-p$? c, $Ar = C_6H_4NO_2-o$; d, $Ar = C_6H_4NO_2-p$

Structure of (VI) was confirmed by: i) IR spectra showed bands at ν_{\max} 1680 (CO) and 1650 cm^{-1} (C=N) and no absorption bands due to ν NH. ii) PMR of (VIb) showed signals (δ) at 3.9 (s, 3H, $-OCH_3$), 5.4 (s, 2H, $-CH_2-O-C_{10}H_7$), 7.0-8.2 (m, 15H, aromatic protons) and 9 (s, 1H, $N=CH-C_6H_4-OCH_3-p$).

Also (Va) reacted with phosphorus pentasulphide in refluxing pyridine to give 2-(2'-naphthyloxymethyl)-3-amino-4(3H)-quinazolinthione (VII)

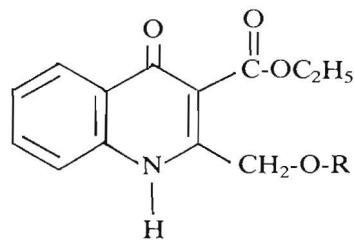


IR spectrum of compound (VII) exhibited bands at $1325 \nu_{\max} \text{ C=S}$, $1635 \nu_{\text{C=N}}$ and $3250 \text{ cm}^{-1} \nu_{\text{NH}}$.

Sammour *et al.* (1973), El-Hashash and Sayed (1978), and El-Hashash *et al.* (1977) reported that 2-substituted benzoxazines react with ethyl acetoacetate, ethyl cyanoacetate or diethyl malonate in presence of sodium ethoxide to give 3-carbethoxy-2-substituted benzo [b]-4-pyridone.

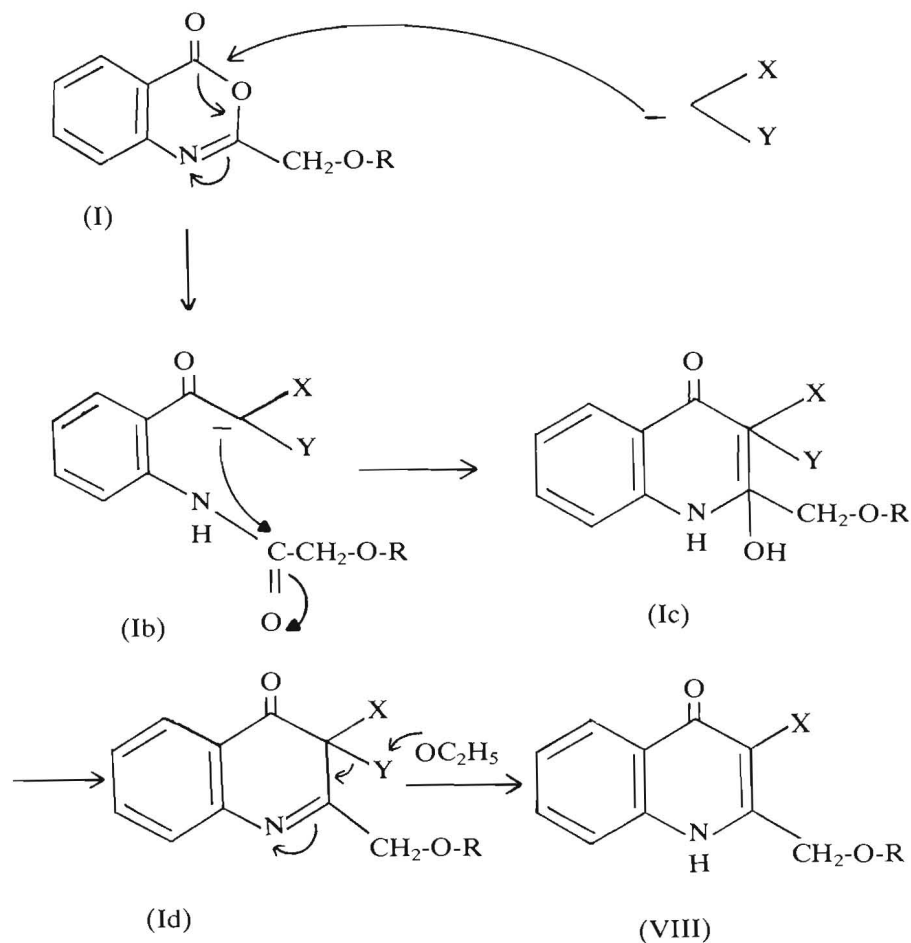
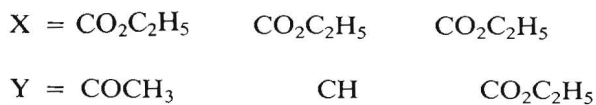
In this investigation the authors tried to study the behaviour of 2-(2'-naphthyloxymethyl)-4H-3, 1-benzoxazin-4-one (I) towards active methylene compounds under Michael conditions.

The benzoxazinone (I) reacted with ethyl acetoacetate, ethyl cyanoacetate or diethyl malonate (El-Hashash and Sayed 1978, Sammour *et al.* 1973, El-Hashash *et al.* 1977, Essawy *et al.* 1982, and Ismail *et al.* 1981) in the presence of sodium ethoxide as a catalyst and yielded one product, 3-carbethoxy-2-(2'-naphthyloxy-methyl)-benzo[b]-4-pyridone (VIII) with the above active methylene compounds.



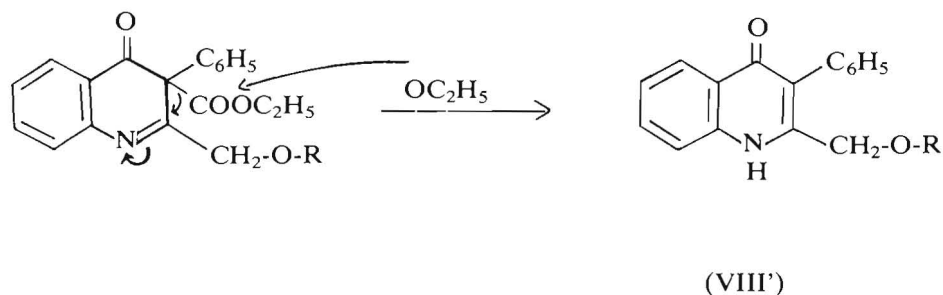
(VIII)

This result can be explained by heterocyclic ring opening by the carbanion of the active methylene. This ring fission is followed by deacetylation or elimination of cyano, or carbethoxy groups respectively and then condensation takes place to give compound (VIII) as the following mechanism:



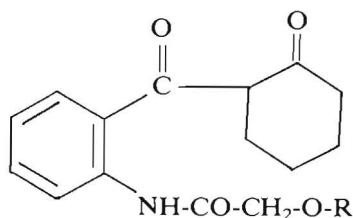
The following support the structure assigned for (VIII): i) IR spectrum showed ν_{\max} 1660 (CO), 1680 (C=O ester), 1620 (C=C) and 3230 cm^{-1} (NH). ii) PMR showed signals (δ) at 1.3 (t, 3H, $-\text{CH}_2-\text{CH}_3$), 4.3 (q, 2H, $-\text{O}-\text{CH}_2-\text{CH}_3$), 4.8 (s, 2H, $-\text{CH}_2-\text{O}-$) and at 7.3 - 8.2 (m, 11H, aromatic protons).

Ethyl phenylacetate readily added to benzoxazinone (I) in the presence of sodium ethoxide to give 3-phenyl-2-(2'-naphthylloxymethyl)-benzo[b]-4-pyridone (VIII') according to the above mechanism with elimination of carboxy group.



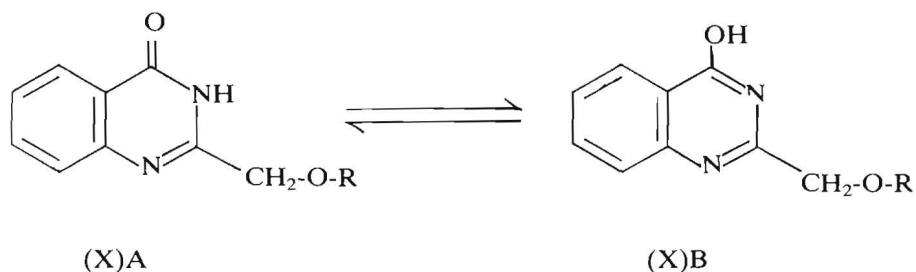
I.R. spectrum of (VIII') showed ν_{\max} 1665 (C=O), 1620 (C=C) and 3250 cm^{-1} (NH), and no absorption band due to $\nu_{\text{C=O}}$ ester. PMR of (VIII') showed signals (δ) at 4.8 (s, 2H, $-\text{CH}_2\text{-O-}$) and at 7.4 - 8.1 (m, 16 H, aromatic protons).

However, the reaction of compound (I) with cyclohexanone in the presence of sodium ethoxide as a catalyst gave N-(2'-naphthyloxyacetyl)anthraniloyl cyclohexanone (IX).



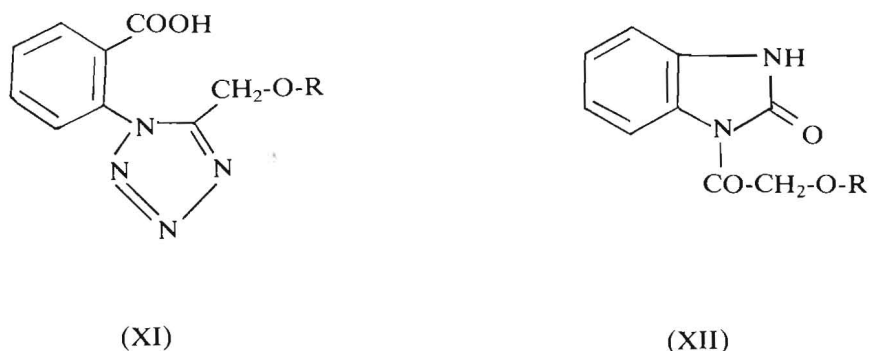
i) IR spectrum of (IX) exhibited bands at 1700, 1680, 1670 and 3220 cm^{-1} due to $\nu_{\text{C=O}}$ (cyclohexanone), $\nu_{\text{C=O}}$ (ketone), $\nu_{\text{C=O}}$ (amide) and ν_{NH} respectively. ii) PMR showed signals (δ) at 4.9 (s, 2H, $-\text{COCH}_2\text{-O-}$), 3.4 (s, 1H, $-\text{C-CH-C-}$), 2.3 (t, 2H, $-\overset{\text{O}}{\parallel}{\text{C-CH}_2}$), 1.8 (m, 6H, $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-}$) and at 7.3-8.1 (m, 11H, aromatic protons).

As a point of interest, compound (I) reacted with formamide (Essawy *et al.* 1982) by fusion at 170°C , and yielded 2-(2'-naphthyloxymethyl)-4(3H)-quinazolinone (X) *via* aminolysis followed by cyclization

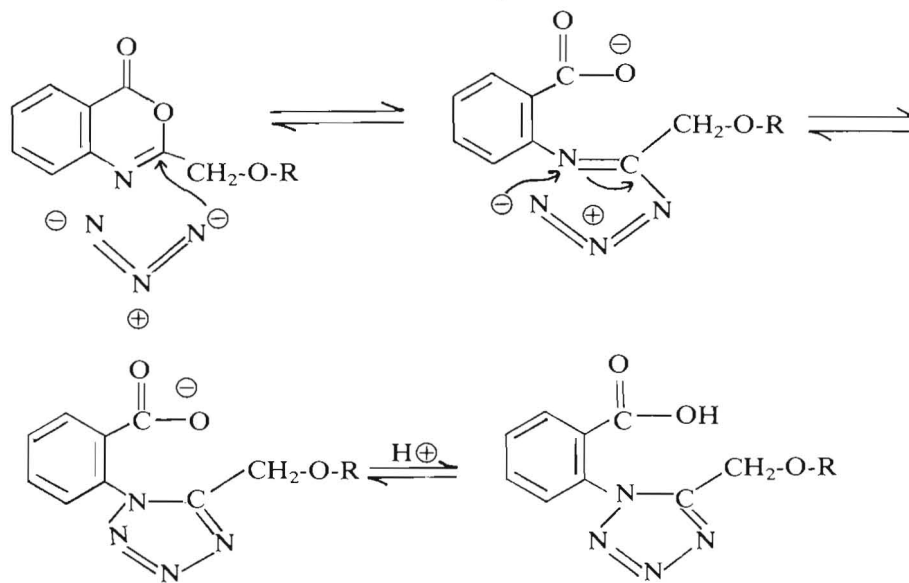


The assigned structure (X) was supported by: i) IR spectrum showing ν_{\max} 3410 (OH), 3100 (NH), 1690 (C=O) and 1640-1620 cm^{-1} (2C=N), such infrared data illustrate that compound (X) actually exists in a lactam-lactim tautomeric equilibrium (XA and XB). ii) PMR showed signals (δ) at 5.1 (s, 2H, $-\text{CH}_2\text{-O-}$), 3.4 (s, 1H, OH proton) and 7.4-8 (m, 11H, aromatic protons).

In this investigation, the hitherto unknown reaction of sodium azide (El Hashash *et al.* 1977, Essawy *et al.* 1982 and Ismail *et al.* 1981) with compound (I) was discovered, thus, benzoxazinone (I) reacted with sodium azide in boiling acetic acid and yielded a mixture of 1-(2-carboxyphenyl)-2-(2'-naphthyloxymethyl)-tetrazole (XI) and 2'-naphthyloxyacetylbenzimidazolone (XII) which might be formed through ring opening either at carbon 3 to give the tetrazole (XI) or at carbon 1 to give the benzimidazolone (XII).

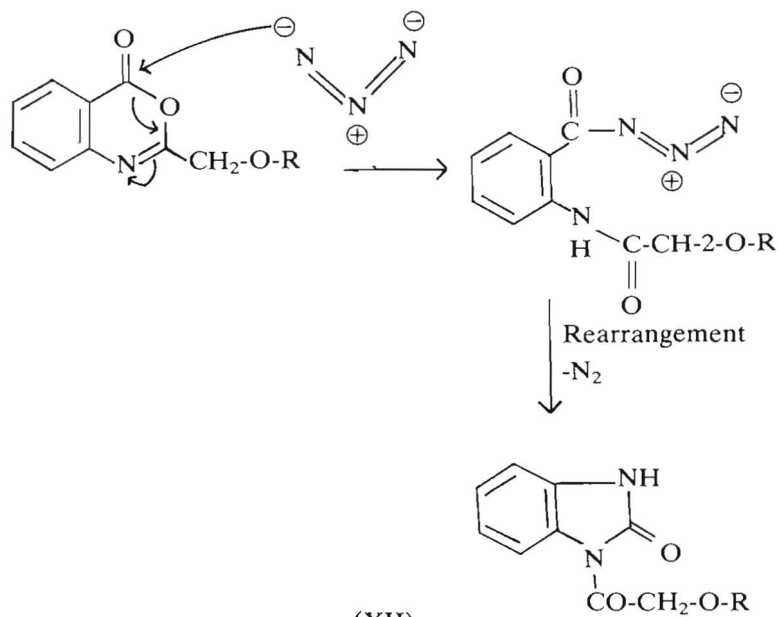


The following support the structure assigned for the tetrazole (XI) and benzimidazolone (XII): i) IR spectrum of (XI) showed ν_{\max} 1730 (C=O of acid), 3390 (OH) and 1060 cm^{-1} (tetrazole) while IR spectrum of (XII) exhibited ν_{\max} 1700-1660 (C=O) and 3300 cm^{-1} (NH). ii) Formation of (XI) possibly takes place according to the following mechanism:



(XI)

iii) Formation of benzimidazolone (XII) possibly takes place according to the following mechanism:



(XII)

From all the above facts we conclude that azidolysis of compound (I) involves ring opening of C₂-O bond, contrary to the normal ring opening of the benzoxazinone ring (fission of C₄-O) bond with all other carbon and nitrogen nucleophiles, because azidolysis involves, 1,3-dipolar cycloaddition to (-N=C₂ bond) while carbon and nitrogen nucleophiles attack the nucleophilic center (-C₂-O-).

Experimental

All melting points reported are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam Spectrophotometer (ν_{\max} in cm^{-1}). NMR spectra in CDCl_3 were run on a Varian VN (S 60 T) instrument using TMS as the internal reference (chemical shifts in δ scale).

Action of Primary Amines or Sec-Amine on 2-(2'-Naphthyloxymethyl)-4H-Benzoxazine-4-One (I): Formation of (IIa-c) and (IV)

A solution of (I) (0.01 mole) and primary amine, namely, butylamine, benzylamine, p-toluidine or secondary amine (piperidine) (0.01 mole) in 60 ml benzene was heated under reflux for 5 hrs, the products (IIa - c) and (IV) that separated on cooling were crystallized from the suitable solvent, the results are listed in Table 1.

Action of Aniline on (I): Formation of (III)

A solution of (I) (0.01 mole) and aniline (0.01 mole) in 60 ml dry benzene in the presence of one ml phosphorus oxychloride was heated under reflux for 8 hrs. The product that separated on cooling was crystallized from a suitable solvent to give compound (III) (cf. Table 1).

Action of Hydrazines on (I): Formation of (Va and b)

A solution of benzoxazinone (I) (0.01 mole) and hydrazine hydrate or phenylhydrazine (0.015 mole) in 50 ml butanol was heated under reflux for 5 hrs in the case of hydrazine hydrate and 12 hrs in the case of phenylhydrazine. The solid separated on cooling was crystallized from the suitable solvent to give (Va and b) respectively (cf. Table 1).

Condensation of the Quinazolinone (Va) with Aromatic Aldehydes: Formation of (VIa - d)

A solution of (Va) (0.01 mole) and aromatic aldehydes namely, p-chlorobenzaldehyde, anisaldehyde, 2-nitrobenzaldehyde, or p-nitrobenzaldehyde in 60 ml butanol was heated under reflux for 6 hrs. The solid separated on cooling was crystallized from the proper solvent to give (VIa - d) respectively (cf. Table 1).

Action of Phosphorus Pentasulphide on (Va): Formation of (VII)

A solution of (Va) (0.01 mole), phosphorus pentasulphide dry pyridine (50 ml) was heated under reflux for 6 hrs. The reaction mixture was concentrated and poured into ice/cold HCl. The solid product that separated was crystallized from ethanol to give (VII) (*cf.* Table 1).

Reaction of (I) with Active Methylene Compounds: Formation of (VIII)

A mixture of benzoxazinone (I) (0.01 mole) and active methylene compounds namely, ethyl acetoacetate, ethyl cyanoacetate or diethyl malonate, (0.02 mole), (0.03 mole) sodium ethoxide in 100 ml absolute ethanol was heated under reflux for 10 hrs. The reaction mixture was poured into ice-cold dil. HCl to give solid product which was crystallized from ethanol to give (VIII) (*cf.* Table 1).

Reaction of (I) with Ethyl Phenylacetate: Formation of (VIII')

A mixture of (I) (0.01 mol), ethyl phenylacetate (0.03 mol) and sodium ethoxide (0.03 mol) in 100 ml absolute ethanol was heated under reflux for 15 hr, poured into cold hydrochloric acid, and the solid formed filtered and crystallised from butanol to give (VIII'), (*cf.* Table 1).

Addition Reaction of Cyclohexanone to Benzoxazinone (I) in the presence of Sodium Ethoxide: Formation of (IX)

A mixture of benzoxazinone (I) (0.01 mol), cyclohexanone (0.02 mol) and sodium ethoxide (0.03 mol) in 50 ml absolute ethanol was heated under reflux for 10 hr. The reaction mixture was cooled and washed with dilute hydrochloric acid 20%. The solid was filtered off and crystallized from ethanol to give compound (IX), (*cf.* Table 1).

Action of Formamide on Benzoxazinone (I): Formation of Quinazolone (X)

A mixture of benzoxazinone (I) (0.01 mole) and formamide (0.015 mole) was heated at 170°C in oil bath for 5 hrs. The product obtained was crystallized to give (X) (*cf.* Table 1).

Action of Sodium Azide on Benzoxazinone (I): Formation of Tetrazole (XI) and Benzimidazolone (XII)

A mixture of benzoxazinone (I) (0.01 mole) and sodium azide (0.015 mole), in boiling acetic acid (40 ml) was refluxed for 5 hrs, cooled and the solid separated filtered and crystallised from ethanol to give (XII). The filtrate was diluted with water to give (XI) which was crystallized from toluene (*cf.* Table 1).

Table 1. Physical data of various compounds prepared

Compd.	M.p. °C	Yield % solvent for crystn.*	Mol. formula (M.Wt.)		Analysis (%)	
					Calcd.	Found
II _a	173	70 (B)	C ₂₃ H ₂₄ N ₂ O ₃ (376)	C	73.40	73.45
				H	6.38	6.45
				N	7.44	7.37
II _b	207	75 (B)	C ₂₆ H ₂₂ N ₂ O ₃ (410)	C	76.09	76.08
				H	5.36	5.38
				N	6.82	6.87
II _c	154	68 (B)	C ₂₆ H ₂₂ N ₂ O ₃ (410)	C	76.09	76.30
				H	5.36	5.40
				N	6.82	6.87
III	170	70 E+P/B	C ₂₅ H ₁₈ N ₂ O ₂ (378)	C	79.36	79.37
				H	4.76	4.78
				N	7.40	7.50
IV	191	70 (E)	C ₂₄ H ₂₄ N ₂ O ₃ (388)	C	74.22	74.32
				H	6.18	6.20
				N	7.21	7.30
V _a	212	60 (T)	C ₁₉ H ₁₅ N ₃ O ₂ (317)	C	71.92	71.80
				H	4.73	4.37
				N	13.24	13.15
V _b	246	50 (X)	C ₂₅ H ₁₉ N ₃ O ₂ (393)	C	76.33	76.32
				H	4.83	4.75
				N	10.68	10.60
VI _a	170	65 (Bu)	C ₂₆ H ₁₈ N ₃ O ₂ Cl (439.5)	C	70.99	70.72
				H	4.09	4.12
				N	9.55	9.00
VI _b	190	70 (Bu)	C ₂₇ H ₂₁ N ₃ O ₃ (435)	C	74.48	74.38
				H	4.82	4.79
				N	9.65	9.63

Table 1. (contd.)

Compd.	M.p. °C	Yield % solvent for crystn.*	Mol. formula (M.Wt.)		Analysis (%)	
					Calcd.	Found
VIc	202	75 (B)	C ₂₆ H ₁₈ N ₄ O ₄ (450)	C	69.33	69.20
				H	4.00	4.01
				N	12.44	12.43
VI _d	186	70 (Bu)	C ₂₆ H ₁₈ N ₄ O ₄ (450)	C	69.33	69.32
				H	4.00	4.01
				N	12.44	12.39
VII	145	50 (E)	C ₁₉ H ₁₅ N ₃ OS (333)	C	68.46	68.34
				H	4.50	4.56
				N	12.61	12.70
				S	9.60	9.63
VIII	125	60 (E)	C ₂₃ H ₁₉ NO ₄ (373)	C	73.99	73.93
				H	5.09	5.12
				N	3.73	3.72
VIII'	145	50 (Bu)	C ₂₆ H ₁₉ NO ₂ (377)	C	82.75	82.81
				H	5.03	5.06
				N	3.71	3.73
IX	160	55 (E)	C ₂₅ H ₂₃ NO ₄ (401)	C	74.81	74.82
				H	5.73	5.69
				N	3.49	3.45
X	223	55 (E)	C ₁₉ H ₁₄ N ₂ O ₂ (302)	C	75.49	75.30
				H	4.63	4.62
				N	9.27	9.44
XI	145	40 (T)	C ₁₉ H ₁₄ N ₄ O ₃ (346)	C	65.89	65.65
				H	4.04	4.02
				N	16.18	16.12
XII	65	20 (E)	C ₁₉ H ₁₄ N ₂ O ₃ (318)	C	71.69	71.65
				H	4.10	4.42
				N	8.80	8.73

B = Benzene, P/B = Light petrol (80-100)/Benzene, T = Toluene
E = Ethanol, X = Xylene and Bu = Butanol

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بعض تفاعلات مع ٢ - (٢ - نفييلوكسي مثيل) - ٤ يد - ٣, ١ - بنزواكزازين - ٤ - أون

عادل منصور الجندي و ماهر الصفتي و عبدالنبي عيسوى
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يشتمل هذا البحث على تفاعل البنزواكزازون (I) مع الأمينات الأولية والثانوية لتكوين الكربامويل أسيتانيليد (II a-c) و (IV) على التوالي غير أنه يتفاعل مع الانيلين في وجود (POCl₃/benzene) لكي يعطي مشتق الكينازولون (III). كذلك تم تفاعل المركب (I) مع الهيدرازينات وأعطى مشتقات الكينازولونات (V a & b) ومن ناحية أخرى تكاثف المركب (V a) مع الألدهيدات الاروماتية وأعطى مشتقات البنزليدين للكينازولون (VI a-d) على التوالي. وقد وجد أن تفاعل مركبات المثيلين النشطة مع المركب (I) في وجود الايثوكسيد كعامل حفاز يؤدي إلى تكوين مركب واحد هو مشتق البنزو (ب) بيريدون (VIII) ولكن مع مركب الهكسانون الحلقي أعطى المركب (IX)، ويتفاعل المركب (I) أيضاً مع الفورماميد وأزيد الصوديوم لكي يعطي المركبات (X) (XI) و (XII) على التوالي لكي يتفاعل المركب (V a) مع خامس كبريتيد الفوسفور ليعطي المركب (VII).