Pakistan J. Sci. Ind. Res., Vol. 25, No. 4, August, 1982

SOME REACTIONS ON 3[2′-(4′H, 2′, 1′)-BENZOXAZIN-4′-ONYL] COUMARINS AND 3(2′-QUINAZOL-4′-ONYL)COUMARINS

M.A. El-Hashash, A.M. Kaddah, M. El-Kady and M.M. Ammer

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo-Egypt

(Received January 27, 1981; revised February 21, 1982)

3(2′-Quinazol-4′-onyl) coumarin (II) was obtained by fusion of 3(2′-(4′H, 3′, 1-benzoxazin)-4′ onyl)coumarin (I) with ammonium acetate or formamide by fusion at 190°. II reacts with benzoyl chloride or phosphorus oxychloride yielding the corresponding 4′-substituted quinazolines derivatives (III). I reacts with amines giving the corresponding anilide derivatives (V). I or II reacts with hydrazine hydrate to give salicylazines (VII) and pyrazolinone (VIII). Michael reaction of I with ethylacetoacetate, diethylmalonate or acetylacetone gives pyranobenzopyrandiones (IX) or 3, 4-disubstituted 3,4-dihydrocoumarin (X). I and IIIb react with sodium azide to give tetrazole derivatives (XI and VI).

INTRODUCTION

Recently the coumarin, 3,1-benzoxazin-4-one and quinazolones have become of increasing importance, being antifungal [1], anticoagulant [2], antispasmodic [3], anticholerostatic [4], molluscacide [5], analgesic [6], potential anti-convulsants [7] and long acting sedatives [8].

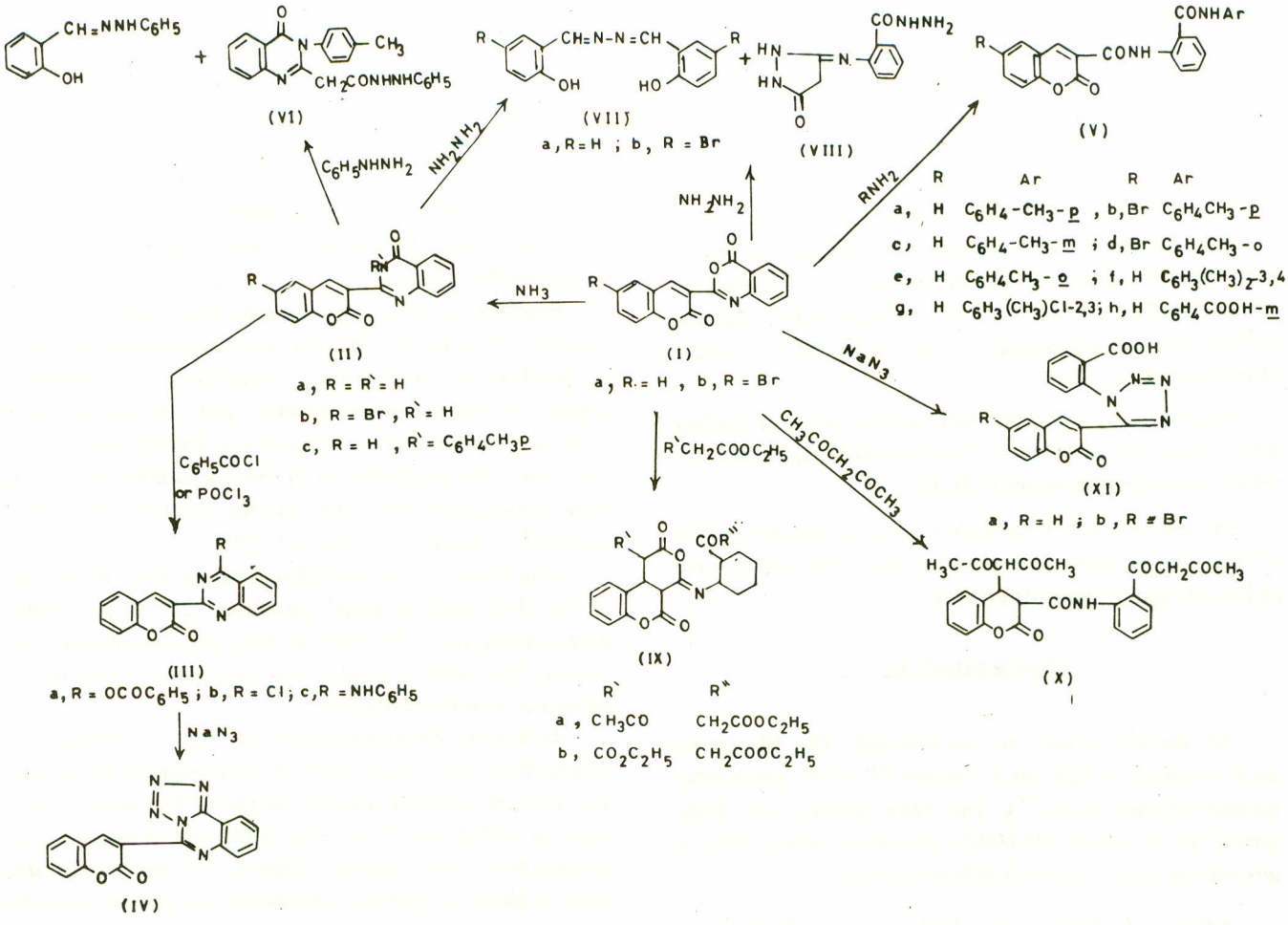
As an extension of our previous work on the 3(3′, 1′ benzoxazin-4′-one)-6-substituted coumarins [9] and 2-substituted 4H-3, 1-benzoxazin-4-one [10, 11], in the present investigation, the study of the behaviour of both α-pyrone and oxazinone or quinazolone rings in 3[2′-(4′H, 3′, 1′-benzoxazin)-4′-onyl)] -coumarins (Ia, b) and 3(2′-quinazol-4′-onyl)coumarins (II) toward different reagents. It was previously stated [9] that Ia reacts with ammonia furnished from ammonium acetate or urea in boiling ethanol to give 3N(2′-carbamidocarbonyl)-coumarin. The present investigation deals with ammonolysis of Ia, b with ammonia furnished from ammonium acetate or formamide in the presence of anhydrous zinc chloride by fusion in oil bath to give 3(2′-quinazol-4′-only)coumarins (IIa, b). The formation of II may be interpreted from the fact that the ammonia furnished from ammonium acetate or formamide reacts readily with the oxazinone ring only [12]. The IR spectra of II showed bands at 1735–1720 (CO of δ-lactone), 1700–1660 (CO of lactam-lactim equilibrium) and3250, 3400 (NH or OH).

The keto-enol tautomerism of II was further demonstrated by the treatment of II with benzoyl chloride or phosphorus oxychloride giving the corresponding 3[2′-(4-substituted)-quinazolinly] coumarins (IIIa, b). Also the reaction of IIIb with aniline or sodium azide in dimethyl formamide give IIIc and 3[2′-(3′, 4′-tetrazolyl)-quinazolinyl-coumarin (IV) respectively.

The structure of III was supported by their IR spectra which showed bands in region 1735–1717 and 1680–1650 due to νCO of δ-lactone and cyclic C=N respectively. The IR spectrum of IV showed bands at (1080) tetrazole [11], (1725) ν CO of δ-lactone and (1625) ν C=N.

The benzoxazonyl coumarin (Ia, b) react with amines namely *p*-toluidine [10], *m*-toluidine, *o*-toluidine, 3,4-dimethyl aniline, 6-chloro-2-aminotoluene or *m*-amino-benzoic acid and yielded 3(2′-N-aryl carbamido-anilino)-coumarins (ν a–h). The formation of V may be interpreted from the fact that amines react readily with fission of the oxazinone ring and not with α-pyrone. The following support the structure assigned for the products V. The products are insoluble in aqueous sodium hydroxide solution and do not give colour reaction with alcoholic ferric chloride solution. V readily hydrolyses [13] on heating with acetic acid and hydrochloric acid mixture or with 50 % sulphuric acid giving the corresponding 6-substituted coumarin carboxylic acid [14, 15] and the corresponding amine salts.

The IR spectra of V do not show hydroxyl absorption and reveal the presence of δ-lactone (1733–1720), CO of amide (1680–1620) and NH (3290–3100). Also the compound Va was converted to the corresponding 3(2′-N-p-tolylquinazol-4′-onyl) coumarin (IIc) by dehydra-



tion with acetic anhydride. The IR spectrum of IIc showed strong absorption bands at 1735 (νCO of lactone), 1680 (νCO of quinazolone) and 1630 (νC=N).

Recently, it has been found that α-pyrone ring can be opened by hydrazines. The IIc reacts with phenylhydrazine (in molar ratio 1:2) in alcohol at room temperature for 3 days or at the boiling point of mixture for 5 hr with the formation of quinazolone (VI) and salicylaldehyde phenylhydrazone. The formation of (VI) can be readily interpreted from the fact that the phenylhydrazine reacts readily with fission of δ-lactone ring and not quinazolone ring. The IR spectrum of VI shows CO of amide at (1640–1660), C=C, C=N (1610) and NH at (3280, 3240 and 3040). The NMR spectrum showed an absorption centered at 2.1 for *2H* (of $-CH_2$-CO) at 2.6 *3H* (for Ar-CH_3) and a broad absorption centered at 6.8 *13H* (of aromatic protons). In preparative support of the structural assignment of salicyaldehyde phenylhydrazone, it can be prepared by independent synthesis from salicyaldehyde and phenyl hydrazine by means of melting point and mixed melting point determination.

On the other hand treatment of Ia, b or IIa, b with hydrazine hydrate in boiling alcohol gave the corresponding salicyalazine (VIIa, b) [14, 15] and 5(2′-carboxyhydrazide) anilinopyrazolin-3-one (VIII). The IR spectrum of VIII shows CO of amide (1620) and NH or OH (broad at 3100–3290). NMR spectrum showed multiplet at 2.4 for *5H*(CH_2 and 3H of NH), multiplet at 6.7 for *4H* (aromatic protons) and multiplet broad at 7.7 for *1H* (CO*NH*).

Recently, Sammour *et al.* [16] found that the ethyl acetoacetate underwent Michael addition to the olefinic C_3-C_4 in coumarin to give pyranobenzopyrantrione. Also El-Hashash [11, 12] reported that 2-substituted benzoxazones react with ethyl acetoacetate, ethyl cyanoacetate and diethyl malonate to give the N-substituted anthraniloylacetate. Similarly the present work investigated the behaviour of Ia toward active methylene compounds under Michael conditions. The reaction of Ia with ethyl acetoacetate and diethyl malonate at 180° in the presence of sodium ethoxide yielded 3-acetyl (carbethoxy)-1, 2-4a-tetrahydro-4(2′-substituted phenyl) imino-pyrano-(3, 4*c*) [1] - benzopyran-2, 5-diones (IX). This result can be ex-

plained by the addition of the active methylene compound to ∝-pyrone and opening the oxazinone ring followed by ring closure and elemination of acetyl or carbethoxy group to give (IX). The IR spectra of IX show strong absorption bands at 1735–1740 (CO of lactone and ester), 1690 (CO of ketone) and 1665 (exocyclic C=N).

But Ia reacts with acetylacetone giving 3(2′-acetoacetylphenyl) carbamide-4-acetylacetonyl-3, 4-dihydrocoumarin (X). The IR spectrum of (X) shows CO of lactone (1735), CO of B-diketone (1690–1670), CO of amide (1640) and NH (3170).

Oxazones Ia, b reacted with sodium azide in boiling acetic acid and yielded 1-2′-carboxyphenyl)-2-(6-substituted coumarinyl)-tetrazole (XIa, b).

IR spectra of XI showed C=O of δ-lactone (1740-1750), CO of aryl acid (1690-1675), C=N (1640) and OH (3200 and of tetrazole (1055).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded in KBr on a Unicam SP 1200 spectrophotometer (λ max in cm^{-1}). The NMR spectra were determined by A varian (60-MHZ) instrument using TMS as internal standard (chemical shift in δ-scale).

Action of Ammonium Acetate or Formamide on Ia, b. A mixture of I (0.01 mol) and ammonium acetate (0.04 mol) or formamide (0.015 mol) was heated at 190° for 3 hr, the whole mass was poured into water. The product was crystallized from a suitable solvent to give IIa, b (Table 1).

Action of Benzoyl Chloride on IIa. A mixture of IIa (0.01 mol) and benzoyl chloride (10 ml) was heated on a water-bath for 2 hr, excess of benzoyl chloride was removed. The whole mass was poured upon water and boiled then filtered hot to get rid of benzoic acid which may be formed. The product obtained was crystallized from the proper solvent giving IIIa (Table 1).

Action of Phosphorus Oxychloride on IIa. A suspension of IIa (1 g) and $POCl_3$ (5 ml) was heated on a water-bath for 2 hr. The reaction mixture was poured gradually into crushed ice and the solid separated was filtered and crystallized from the suitable solvent to give IIIb as reddish brown crystals (Table 1).

Reaction of IIIb with Aniline. A suspension of IIIb (0.01 mol) and aniline (0.01 mol) was heated on a water-bath for 3 hr. The reaction mixture was treated by crushed ice/HCl, the solid that separated was filtered and crystallized from the suitable solvent giving IIIc (Table 1).

Action of Sodium Azide on IIIb. A mixture of IIIb (0.01 mol), sodium azide (0.05 mol) and diethyl formamide (40 ml) was refluxed for 3 hr. The reaction mixture was poured into water, the solid separated, was filtered off and crystallized from the proper solvent to give the tetrazole derivative (IV) (Table 1).

Reaction of Ia, b with Amines and Amino Acids. A solution of Ia and b (0.01 mol) and primary amines, namely *p*-toluidine, *m*-toluidine, *o*-toluidine, 3, 4-dimethyl aniline, 6-chloro-2-aminotoluene and *m*-benzoic acid (0.01 mol) in (40 ml) of ethanol was heated under reflux for 5 hr. The products Va–h that separated on cooling were crystallized from the suitable solvent. The results are listed in Table 1. Va m.p. 292 [9].

Conversion of Va into Quinazolones IIc. A solution of Va (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 2 hr. The mixture was concentrated and cooled. The solid separated was crystallized from proper solvent to give IIc (Table 1).

Action of Phenylhydrazine on IIc. A solution of quinazolone (IIc) (0.01 mol), phenylhydrazine (0.02 mol) and (50 ml) ethanol was left at room temperature for 3 days or reflux for 5 hr. The solid that separated after concentration and cooling, filtered off, and crystallized from butanol to give the salicyaldehyde phenylhydrazone which was identified by m.p. and mixed m.p. determination. Concentration of the mother liquor left as solid product which was crystallized from light petrol (b.p. 100–120°) to give VI (Table 1).

Reaction of Hydrazine Hydrate with Ia, b and IIa, b. A solution of Ia, b and IIa, b (0.01 mol), hydrazine hydrate (0.03 mol) and ethanol (50 ml) was heated under reflux for 5 hr. The solid that separated after concentrating and cooling was fractionally cystallized from ethanol to give the pyrazolinone (VIII). The insoluble part was crystallized from acetic acid to give products which were identified as salicylazing derivatives (VIIa, b) by m.p. and mixed m.p. determination.

Condensation of Ia with Active Methylene Compounds. A mixture of Ia (0.01 mol), ethyl acetoacetate or diethylmalonate and acetylacetone (0.03 mol) and sodium ethoxide (0.03 mol) was heated at 180 for 4 hr. Then poured upon water, the product separated out was filtered off and crystallized from proper solvent to give the Michael adducts IXa, b and X respectively (Table 1).

Action of Sodium Azide on Ia and Ib. A mixture of Ia or Ib (0.01 mol) and sodium azide (0.05 mol) in acetic acid (40 ml) was refluxed for 3 hr. The product obtained

Table 1. Characterization data of various compounds prepared.

Compd.	M.p (colour)	Solvent (yield%)	Formula	Analysis Found C	H	(Calc.) N
IIa	245 (colourless)	Acetic acid (70)	$C_{17}H_{10}N_2O_3$	70.50 (70.34)	3.50 (3.44)	9.33 (9.65)
IIb[+]	240 (pale yellow)	Ethanol (50)	$C_{17}H_9N_2O_3Br$	55.6 (55.28)	2.31 (2.44)	7.42 (7.58)
IIc	255 (colourless)	Ethanol (60)	$C_{24}H_{16}N_2O_3$	75.52 (75.78)	4.32 (4.21)	7.15 (7.36)
IIIa	137 (pale yellow)	Toluene (70)	$C_{24}H_{14}N_2O_4$	72.98 (73.09)	3.42 (3.55)	7.34 (7.10)
IIIb[*]	254 (yellow)	Ethanol (50)	$C_{17}H_9N_2O_2Cl$	66.16 (66.12)	2.99 (2.91)	8.99 (9.07)
IIIc	275 (yellow)	Benzene (60)	$C_{23}H_{15}N_3O_2$	75.70 (75.61)	4.50 (4.10)	11.70 (11.50)
IV	110 (colourless)	Benzene (50)	$C_{17}H_{19}N_5O_2$	64.50 (64.76)	2.90 (2.85)	22.35 (22.22)
Vb[@]	143 (pale yellow)	Benzene (80)	$C_{24}H_{17}N_2O_4Br$	60.10 (60.37)	3.40 (3.56)	5.50 (5.87)
Vc	244 (pale yellow)	Acetic acid (70)	$C_{24}H_{18}N_2O_4$	72.63 (72.36)	4.32 (4.52)	7.40 (7.03)
Vd[≠]	200 (pale yellow)	Toluene (70)	$C_{24}H_{17}N_2O_4Br$	60.76 (60.37)	3.82 (3.56)	5.40 (5.87)
Ve	230 (pale yellow)	Acetic acid (60)	$C_{24}H_{18}N_2O_4$	72.30 (72.36)	4.31 (4.52)	7.20 (7.03)
Vf	236 (pale yellow)	Toluene (70)	$C_{25}H_{20}N_2O_4$	72.40 (72.81)	4.61 (4.85)	6.35 (6.79)
Vg[≠@]	260 (colourless)	Acetic acid (50)	$C_{24}H_{17}N_2O_4Cl$	66.20 (66.58)	4.01 (3.93)	7.00 (6.47)
Vh	290 (colourless)	Butanol (50)	$C_{24}H_{16}N_2O_6$	66.98 (67.28)	3.50 (3.73)	6.31 (6.54)

Continued.....

VI	130 (pale yellow)	Light pet. (100-120) (40)	$C_{23}H_{20}N_4O_2$	71.62 (71.87)	5.43 (5.20)	15.01 (14.58)
VIII	139 (orange)	Benzene (30)	$C_{10}H_{11}N_4O_2$	55.11 (54.79)	5.30 (5.02)	25.22 (25.27)
IXa	158 (colourless)	Ethanol (40)	$C_{25}H_{21}NO_8$	64.31 (64.79)	4.21 (4.53)	6.32 (6.02)
IXb	274 (colourless)	Acetic acid (30)	$C_{26}H_{23}NO_9$	63.62 (63.28)	4.31 (4.66)	6.01 (5.67)
X	240 (colourless)	Acetic acid (50)	$C_{25}H_{23}NO_7$	67.20 (66.81)	5.40 (5.10)	3.33 (3.11)
XIa	270 (colourless)	Acetic acid (70)	$C_{17}H_{10}N_4O_4$	60.89 (61.07)	8.01 (2.99)	16.45 (16.76)
XIb	175 (yellow)	Toluene (40)	$C_{17}H_9N_4O_4Br$	49.52 (49.39)	2.41 (2.17)	13.21 (13.55)

+ Found Br, 20.90; calc, Br. 21.68; * Found Cl, 11.02; calc. Cl, 11.50; @ Found Br, 16.51; calc, Br. 16.77; ≠ Found Br, 17.20, calc. Br, 16.77; ≠ @ Found Cl, 8.63, calc. Cl, 8.20.

after concentration and pouring upon water was recrystallized from proper solvent to give tetrazole XIa and b (Table 1).

REFERENCES

1. D.P. Chakraborty, A. Gupta and P.K. Bose, Ann. Biochem. Exp. Med., **17**, 57 (1957).
2. R.B. Arora, C.N. Mathur, Br. J. Pharmacol., **20** 29 (1963), K.P. Link, Harv. Lect., **39**, 162 (1943).
3. R.E. Willette and T.O. Soine, J. Pharm. Sci., **51**, 149 (1962).
4. D. Molho, E. Boschetti and L. Fontaine, U.S. Patent 3175943 (1965); C.A., **64**, 14040 (1966).
5. A. Schenberg and N. Latif, J. Am. Chem. Soc., **76**, 6208 (1954).
6. Ott, Hans, Swiss 491, 134 (1970); C.A. **73**, 120668 (1970).
7. P.M. Bhargava, N.M. Khanna and M.L. Dhar, Ind. J. Chem. **2**, 159 (1964).
8. C. Runti, C. Nisi, and L. Sindellaria, Ann. Chim. Rome., **51**, 719 (1961).
9. M.M. Abdella, M. El-Kady and A.F. El-Farargy, Egypt J. Chem., **20**, 245 (1977).
10. M.A. El-Hashash and M.A. Sayed, Egypt J. Chem., **21**, 115 (1978).
11. M.A. El-Hashash, M.A. Hassan and M.A. Syed, Pakistan, J. Sci and Ind. Res., **20**, 336 (1977).
12. A. Sammour, M.I.B. Selim and M. Anwar abdo, U.A.R. J. Chem., **14**, 197 (1971).
13. P.M. Bhargara and S.L. Zaheer, J. Chem. Soc., 311 (1952).
14. A. Sammour, A. Marie and S. El-Ashry, U.A.R. J. Chem., **13**, 281 (1970).
15. A. Sammour, M.I.B. Selim and M. El-Kady, U.A.R. J. Chem., **14**, 261 (1971).
16. A. Sammour, M. Abdalla and M. El-Kady, Acta Chem. (Budapest), **82**, 369 (1974).