NOVEL SYNTHESIS OF 3-SPIROHETEROCYCLES-2-METHYLQUINOLIN-4-ONE

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2-Methyl[3,1]benzoxazin-4-one (*I*) is easily accessible, but its chemistry has not been investigated enough.

Structure similarity between *I* and phthalic anhydride encouraged us to investigate the reaction of *I* with compounds bearing active methylenes namely diethyl malonate, ethyl acetoacetate and acetylacetone in presence of zinc chloride. Thus new compounds *II*, *III* and *IV* were synthesized. Those compounds were used as precursors for the synthesis of various spiroheterocycles.

EXPERIMENTAL

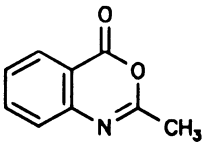
The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr pellets on a Shimadzu IR 470 infrared spectrophotometer. ^{1}H NMR spectra were measured in $(CD_3)_2SO$, chemical shifts are given in ppm (δ-scale). Microanalyses were determined on a Perkin–Elmer 240C microanalyzer. Data for synthesized compounds are given in Table I.

Preparation of 2-Methyl[3,1]benzoxazin-4-one (*I*)

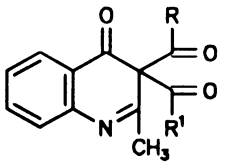
This compound was prepared according to the reported procedure[1].

Synthesis of 3,3-Bis(ethoxycarbonyl)-2-methyl-3,4-dihydroquinolin-4-one (*II*), 3-Acetyl-3-ethoxycarbonyl-2-methyl-3,4-dihydroquinolin-4-one (*III*) and 3,3-Diacetyl-2-methyl-3,4-dihydroquinolin-4-one (*IV*); General Procedure

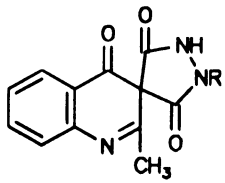
Compound *I* (16.1 g, 0.1 mol) was treated with 16.0 g (0.1 mol) diethyl malonate or 13.0 g (0.1 mol) ethyl acetoacetate or 10.0 g (0.1 mol) acetylacetone in the presence of anhydrous zinc chloride (13.6 g, 0.1 mol) and heated at 160 – 180 °C for 30 min. The reaction mixture was cooled to room temperature, diluted with 200 ml 10% HCl and extracted with chloroform. The chloroform was removed under reduced pressure using rotary evaporator. All the residue separated in each case was triturated with petroleum ether or diethyl ether. The solid products were crystallized from ethanol and afforded pale yellow crystals of *II*, *III* and *IV*, respectively.



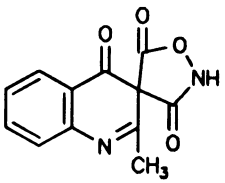
I



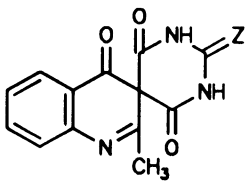
II, R = R' = OC_2H_5
III, R = CH_3; R' = OC_2H_5
IV, R = R' = CH_3



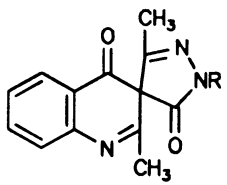
Va, R = H
Vb, R = C_6H_5



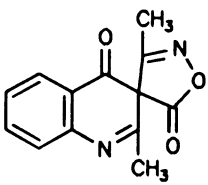
VI



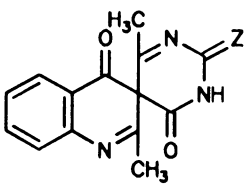
VIIa, Z = O
VIIb, Z = S



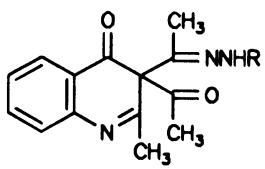
VIIIa, R = H
VIIIb, R = C_6H_5



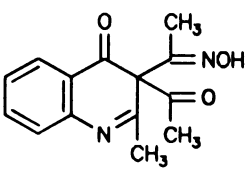
IX



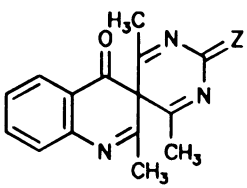
Xa, Z = O
Xb, Z = S



XIa, R = H
XIb, R = C_6H_5



XII



XIIIa, Z = O
XIIIb, Z = S

TABLE I
Physical properties, yields and elemental and spectral analyses of the synthesized compounds

Compound	M. p., °C (Yield, %)	Formula (M. w.)	Calculated/Found				IR, cm^{-1}	^1H NMR, δ ppm
			% C	% H	% N	% S		
II	255 – 257[a] (60)	$C_{16}H_{17}NO_5$ (303.3)	63.36 63.00	5.61 5.20	4.62 4.20	– –	3 025 (CH arom.); 2 920 (CH aliph.); 1 730, 1 680 (C=O); 1 600 (C=N)	1.30 t, 6 H; 2.60 m, 4 H; 2.85 s, 3 H; 7.20 – 7.90 m, 4 H
III	138 – 140[a] (65)	$C_{15}H_{15}NO_4$ (273.3)	65.93 65.60	5.49 5.20	5.12 5.00	– –	3 030 (CH arom.); 2 940 (CH aliph.); 1 720, 1 680 (C=O); 1 600 (C=N)	1.30 t, 3 H; 2.70 m, 2 H; 2.85 s, 3 H; 2.9 s, 3 H; 7.20 – 7.90 m, 4 H
IV	165 – 167[a] (55)	$C_{14}H_{13}NO_3$ (243.2)	69.13 69.00	5.34 5.00	5.76 5.25	– –	3 040 (CH arom.); 2 920 (CH aliph.); 1 720, 1 680 (C=O); 1 620 (C=N)	2.25 s, 6 H; 2.80 s, 3 H; 7.20 – 7.90 m, 4 H
Va	>300[a] (52)	$C_{12}H_9N_3O_3$ (243.2)	59.25 59.00	3.70 3.40	17.28 17.00	– –	3 350 (NH); 3 050 (CH arom.); 2 890 (CH aliph.); 1 715 (C=O); 1 630 (C=N)	2.85 s, 3 H; 4.75 s, 2 H; 7.20 – 7.90 m, 4 H
Vb	172 – 174[b] (50)	$C_{18}H_{13}N_3O_3$ (319.3)	67.71 67.50	4.07 4.00	13.16 13.00	– –	3 400 (NH); 3 040 (CH arom.); 2 920 (CH aliph.); 1 710 (C=O); 1 620 (C=N)	2.80 s, 3 H; 4.70 s, 1 H; 7.00 – 7.70 m, 7 H
VI	180 – 182[a] (60)	$C_{12}H_8N_2O_4$ (244.2)	59.01 59.00	3.27 3.00	11.47 11.20	– –	3 350 (NH); 3 050 (CH arom.); 2 930 (CH aliph.); 1 725 (C=O); 1 620 (C=N)	2.85 s, 3 H; 4.60 s, 1 H; 7.20 – 7.70 m, 4 H

TABLE I
(*Continued*)

Compound	M. p., °C (Yield, %)	Formula (M. w.)	Calculated/Found				IR, cm^{-1}	^1H NMR, δ ppm
			% C	% H	% N	% S		
VIIa	194 – 196[c] (55)	$C_{13}H_9N_3O_3$ (271.2)	57.56 57.20	3.32 3.00	15.49 15.25	– –	3 400 (NH); 3 040 (CH arom.); 2 920 (CH aliph.); 1 700 (C=O); 1 630 (C=N)	2.80 s, 3 H; 4.75 s, 2 H; 7.20 – 7.70 m, 4 H
VIIb	190 – 192[c] (58)	$C_{13}H_9N_3O_3S$ (241.2)	54.35 54.10	3.13 3.00	14.63 14.20	11.14 11.00	3 400 (NH); 3 045 (CH arom.); 2 890 (CH aliph.); 1 710 (C=O); 1 630 (C=N); 1 500 (N–C=S)	2.80 s, 3 H; 4.75 s, 2 H; 7.00 – 7.50 m, 4 H
VIIIIa	266 – 268[b] (54)	$C_{13}H_{11}N_3O_2$ (241.2)	64.73 64.42	4.56 4.30	17.42 17.20	– –	3 400 (NH); 3 050 (CH arom.); 2 940 (CH aliph.); 1 710 (C=O); 1 630 (C=N)	2.80 s, 6 H; 4.70 s, 1 H; 7.00 – 7.50 m, 4 H
VIIIb	128 – 130[d] (56)	$C_{19}H_{15}N_3O_2$ (317.3)	71.92 71.60	4.73 4.30	13.24 13.00	– –	3 040 (CH arom.); 2 920 (CH aliph.); 1 710 (C=O); 1 620 (C=N)	2.80 s, 6 H; 7.00 – 7.80 m, 9 H
IX	160 – 162[e] (48)	$C_{13}H_{10}N_2O_3$ (242.2)	64.46 64.20	4.13 4.00	11.57 11.30	– –	3 040 (CH arom.); 2 920 (CH aliph.); 1 715 (C=O); 1 625 (C=N)	2.80 s, 6 H; 7.00 – 7.60 m, 4 H
Xa	>300[a] (68)	$C_{13}H_{11}N_3O_3$ (257.2)	60.70 60.40	4.28 4.00	16.34 16.00	– –	3 400 (NH); 3 040 (CH arom.); 2 920 (CH aliph.); 1 700 (C=O); 1 630 (C=N)	2.85 s, 6 H; 4.60 s, 1 H; 7.00 – 7.50 m, 4 H

TABLE I
(*Continued*

Compound	M. p., °C (Yield, %)	Formula (M. w.)	Calculated/Found				IR, cm^{-1}	^1H NMR, δ ppm
			% C	% H	% N	% S		
Xb	214 – 216[c] (70)	$C_{13}H_{11}N_3O_2S$ (273.3)	57.14 57.00	4.02 4.00	15.38 15.10	11.72 11.50	3 370 (NH); 3 020 (CH arom.); 2 930 (CH aliph.); 1 710 (C=O); 1 625 (C=N)	2.85 s, 6 H; 4.65 s, 1 H; 7.00 – 7.50 m, 4 H
XIa	>300[e] (72)	$C_{14}H_{15}N_3O_2$ (257.2)	65.36 65.00	5.83 5.50	16.34 16.00	– –	3 500, 3 450 (NH_2); 3 050 (CH arom.); 2 925 (CH aliph.); 1 710 (C=O); 1 620 (C=N)	2.75 s, 6 H; 3.00 s, 3 H; 4.00 broad, 2 H; 7.00 – 7.50 m, 4 H
XIb	222 – 224[f] (55)	$C_{20}H_{19}N_3O_2$ (333.4)	72.07 72.00	5.70 5.30	12.61 12.40	– –	3 370 (NH); 3 030 (CH arom.); 2 890 (CH aliph.); 1 720 (C=O); 1 620 (C=N)	2.75 s, 6 H; 3.00 s, 3 H; 4.10 s, 1 H; 7.00 – 7.80 m, 9 H
XII	>300[a] (52)	$C_{14}H_{14}N_2O_3$ (258.2)	65.11 65.00	5.42 5.20	10.85 10.50	– –	3 500 (OH); 3 030 (CH arom.); 2 920 (CH aliph.); 1 720 (C=O); 1 630 (C=N)	2.75 s, 6 H; 3.00 s, 3 H; 4.5 s, 1 H; 7.00 – 7.50 m, 4 H
XIIIa	179 – 181[e] (55)	$C_{15}H_{13}N_3O_2$ (267.2)	64.41 64.20	4.86 4.40	15.73 15.30	– –	3 050 (CH arom.); 2 890 (CH aliph.); 1 720 (C=O); 1 630 (C=N)	2.85 s, 9 H; 7.00 – 7.50 m, 4 H
XIIIb	245 – 247[a] (60)	$C_{15}H_{13}N_3OS$ (283.2)	63.60 63.40	4.59 4.30	14.84 14.60	11.30 11.00	3 040 (CH arom.); 2 920 (CH aliph.); 1 725 (C=O); 1 620 (C=N)	2.85 s, 9 H; 7.00 – 7.50 m, 4 H

Crystallized from [a] ethanol, [b] ethanol–water (1 : 1), [c] methanol, [d] chloroform–petroleum ether (1 : 3), [e] water, [f] dichloromethane.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-4′-(3′,5′-dioxopyrazolidine) (*Va*) and
(2-Methyl-3,4-dihydroquinolin-4-one)-spiro-4′-(1′-phenyl-3′,5′-dioxopyrazolidine) (*Vb*)

A mixture of 0.001 mol of *II*, 0.0015 mol of 99% hydrazine hydrate or phenylhydrazine in a mixture of ethanol–pyridine 3 : 1 was refluxed for 4 h. Compounds *Va* and *Vb*, respectively, were obtained after the concentration of the reaction mixture, cooling and pouring into cold 10% HCl. The products were filtered, separated and crystallized from the proper solvent.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-4′-(3′,5′-dioxoisoxazolidine) (*VI*)

A mixture of 0.001 mol of *II* and 0.0015 mol of hydroxylamine hydrochloride in 15 ml pyridine was refluxed for 5 h. The reaction mixture was cooled and poured into 20 ml of 10% hydrochloric acid to afford *VI*.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5′-(hexahydro-2′,4′,6′-trioxopyrimidine) (*VIIa*) and
(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5′-(hexahydro-4′,6′-dioxo-2′-thioxopyrimidine (*VIIb*)

A solution of 0.001 mol of *II* and 0.0015 mol of urea or thiourea in 25 ml of ethanol–pyridine mixture 3 : 1 was refluxed for 5 h. The reaction mixture was cooled to room temperature, then poured into iced 10% hydrochloric acid solution whereby *VIIa* and *VIIb*, respectively, were separated as pale yellow crystals.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-4′-(3′-methyl-5′-oxopyrazoline) (*VIIIa*) and
(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-4′-(3′-methyl-5′-oxo-1′-phenylpyrazoline) (*VIIIb*)

A mixture of 0.001 mol of *III*, 0.0015 mol of hydrazine hydrate or phenylhydrazine in a mixture of ethanol–pyridine 3 : 1 was refluxed for 5 h. Compounds *VIIIa* and *VIIIb* were obtained after the concentration of the reaction mixture, cooling, pouring into cold dilute hydrochloric acid and filtration.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-4′-(3′-methyl-5′-oxoisoxazolidine) (*IX*)

A mixture of 0.001 mol of *III* and 0.0015 mol hydroxylamine hydrochloride in 15 ml pyridine was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into dilute hydrochloric acid to yield *IX* as pale yellow crystals.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5′-(4′-methyl-2′,6′-dioxo-1′,2′,5′,6′-tetrahydropyrimidine) (*Xa*) and (2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5′-(4′-methyl-6′-oxo-6′-thioxo-1′,2′,5′,6′-tetrahydropyrimidine) (*Xb*)

A solution of 0.001 mol of *III* and 0.0015 mol of urea and thiourea in a mixture of ethanol–pyridine 3 : 1 was refluxed for 4 h, cooled to room temperature, then poured into cold dilute hydrochloric acid whereby *Xa* and *Xb* were separated as pale yellow crystals.

3-Acetyl-3-acetylhydrazone-2-methyl-3,4-dihydroquinolin-4-one (*XIa*) and
3-Acetyl-3-acetylphenylhydrazone-2-methyl-3,4-dihydroquinolin-4-one (*XIb*)

A mixture of 0.001 mol of *IV* and 0.0015 mol of 99% hydrazine hydrate or phenylhydrazine in a mixture of ethanol–pyridine 3 : 1 was refluxed for 5 h. The products were obtained after the concentration of the reaction mixture, cooling and pouring into cold dilute hydrochloric acid, then filtered off to give *XIa* or *XIb*, respectively, as pale yellow crystals.

3-Acetyl-3-(1-hydroximinoethyl)-2-methyl-3,4-dihydroquinolin-4-one (*XII*)

A mixture of 0.001 mol of *IV* and 0.0015 mol of hydroxylamine hydrochloride in 15 ml of pyridine was refluxed for 5 h. The reaction mixture was cooled and poured into 20 ml of dilute hydrochloric acid to give *XII*.

(2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5'-(4',6'-dimethyl-2'-oxo-2',5'-dihydropyrimidine) (*XIIIa*) and (2-Methyl-3,4-dihydroquinolin-4-one)-3-spiro-5'-(4',6'-dimethyl-2'-thioxo-2',5'-dihydropyrimidine) (*XIIIb*)

A solution of 0.001 mol of *IV* and 0.0015 mol of urea or thiourea in a mixture ethanol–pyridine 3 : 1 was refluxed for 4 h and then cooled to room temperature, poured into cold 10% hydrochloric acid solution whereby *XIIIa* or *XIIIb*, respectively, were separated.

REFERENCES

1. Singh P.: J. Indian Chem. Soc. *4*, 801 (1978).