STUDIES IN VILSMEIER–HAACK REACTION. APPLICATION TO QUINOXALINONES

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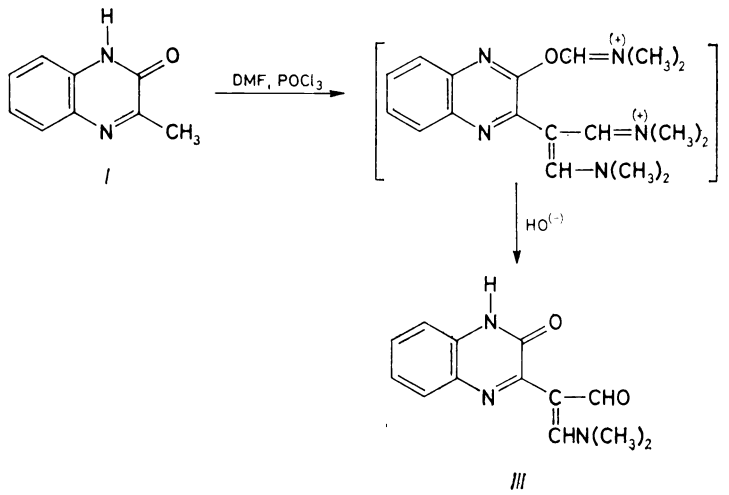
The 3-methyl group in quinoxalinones *I* and *II* has been found to undergo diformylation by Vilsmeier reagent to give the corresponding aminoacrolein derivatives (*III*, *IV*). Condensation and/or interaction of *III* or *IV* with some secondary heterocyclic amines and/or with hydrazine, phenylhydrazine and hydroxylamine affords the related 3-methyl-N-(1*H*)-2-quinoxalinone and 1,3-dimethyl-2-quinoxalinone derivatives (*VII*—*XVIII*), some with pronounced fluorescence activities. All synthesized compounds have been screened in vitro for their antimicrobial activities against Gram-positive and Gram-negative bacteria. The structures of these compounds were confirmed by elemental analysis, IR and ^{1}H NMR spectroscopy.

It was reported[1,2] that some of the heterocycles derived from the product of the Vilsmeier reaction with 2-methyl benzoxazole exhibited fluorescence in daylight. In view of the current interest in fluorescent compounds for use on textile fibres, it was thought of interest to prepare a wide variety of heterocyclic compounds from

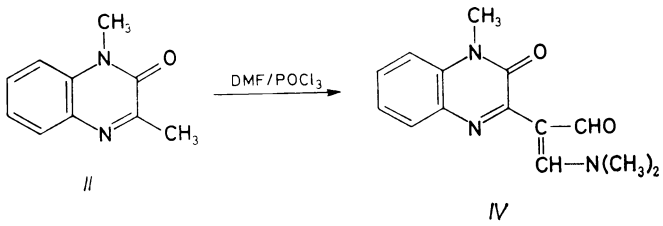


I *III*

SCHEME 1

different azoles and to study their utility as fluorescent whiteners. The foregoing benefits and success met with the application of the title reaction on some active methyl-substituted heterocyclic compounds were an encouraging sign towards further extension of this successful reaction to other heterocyclic systems. Thus, the present paper deals with the behaviour of some 3-methyl quinoxalinones towards Vilsmeier reaction.

Vilsmeier reaction of *I*, *II* was performed under usual conditions and the products obtained were found to be dimethylaminoacroleins *III* and *IV* (Scheme 1 and 2),

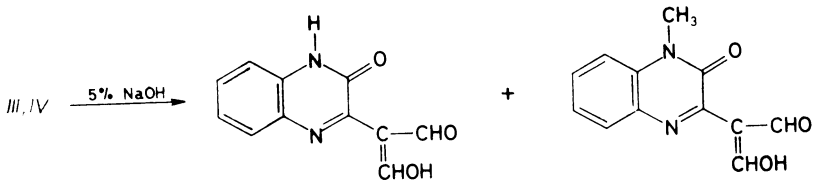


II *IV*

SCHEME 2

as shown by their elemental analysis, IR and ^{1}H NMR spectra and their chemical reactions. It must be pointed out that no chlorination takes place at position 2 under the Vilsmeier reaction conditions. The reaction of 3-methyl quinoxalinone (*I*) with Vilsmeier reagent is postulated to occur through prior attack on the N–H nitrogen. This has been made because of the observation of Naik et al.[3] in the application of Vilsmeier reaction on 2-methyl benzimidazole and 1,2-dimethyl benzimidazole. Attempts were made to isolate the N-formyl derivative of *III* but without success.

Aminoacroleins *III* and *IV* were readily hydrolyzed by heating with 5% caustic soda solution giving the corresponding malondialdehydes *V* and *VI* with evolution of dimethylamine (Scheme 3). Condensation of the aminoacroleins *III* and *IV* with some secondary heterocyclic amines proceeds easily in warm ethanol, giving the expected aminomethylenes *VII*–*XII*, respectively. On the other hand, amino-acroleins *III* and *IV* interact in boiling ethanol with hydroxylamine, hydrazine

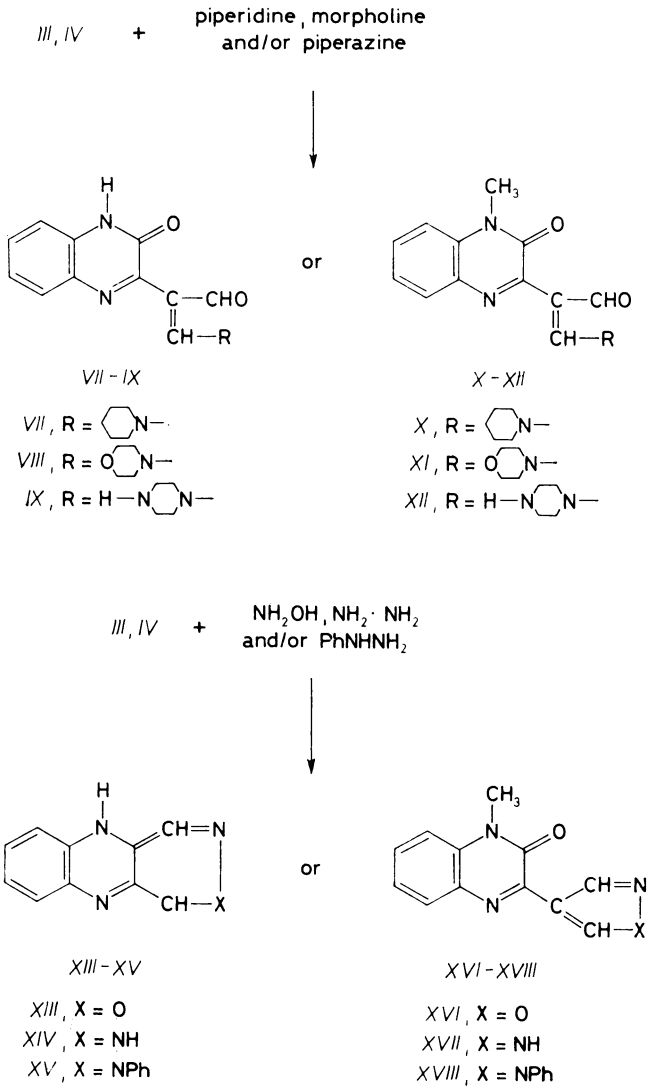


V *VI*

SCHEME 3

hydrate and/or phenylhydrazine, giving the expected heterocyclic systems at the 3-position of the quinoxalinone moiety products (*XIII*–*XVIII*) (see Scheme 4).

The biological screening of all the synthesized compounds (*I*–*XVIII*, Table I) showed variable antibacterial activities against a number of Gram-positive and Gram-negative bacteria used (Table II). The starting materials of quinoxalinone derivatives *I* and *II* showed a mild and/or no antibacterial activities against all of the



SCHEME 4

TABLE I

Physical and analytical data of synthesized compounds (*III*–*XVIII*)

Compound	M.p. °C	Yield %	Formula (M.w.)	Calculated/Found		
				% C	% H	% N
III	308	72	$C_{13}H_{13}N_3O_2$ (243·3)	64·17 64·15	5·39 5·40	17·26 17·30
IV	222	75	$C_{14}H_{15}N_3O_2$ (257·3)	62·36 62·38	5·88 5·85	16·33 16·30
V	290	63	$C_{11}H_8N_2O_3$ (223·3)	59·18 59·20	3·61 3·58	12·55 12·58
VI	210	68	$C_{12}H_{10}N_2O_3$ (230·2)	62·61 62·58	4·38 4·41	12·17 12·21
VII	240	81	$C_{16}H_{17}N_3O_2$ (283·3)	67·83 67·80	6·05 6·10	14·83 14·80
VIII	262	77	$C_{15}H_{15}N_3O_3$ (285·3)	63·15 63·17	5·30 5·33	14·73 14·70
IX	250	68	$C_{15}H_{16}N_4O_2$ (284·3)	63·37 63·32	5·67 5·62	19·71 19·67
X	171	62	$C_{17}H_{19}N_3O_2$ (313·4)	65·16 65·21	6·11 6·14	13·41 13·38
XI	142	69	$C_{16}H_{17}N_3O_3$ (299·3)	64·20 64·17	5·72 5·68	14·04 14·08
XII	180	72	$C_{16}H_{18}N_4O_2$ (298·3)	64·42 64·44	6·08 6·04	18·78 18·71
XIII	220	76	$C_{11}H_8N_4O$ (222·3)	59·43 59·40	8·16 8·19	25·20 25·17
XIV	282	71	$C_{17}H_{12}N_4O$ (288·3)	70·82 70·78	4·20 4·28	19·43 19·40
XV	240	63	$C_{11}H_7N_3O_2$ (213·2)	61·97 61·91	3·31 3·38	19·71 19·68
XVI	246	73	$C_{12}H_{10}N_4O$ (226·2)	63·71 63·73	4·46 4·41	24·76 24·72
XVII	150	68	$C_{18}H_{14}N_4O$ (302·3)	71·51 71·47	4·67 4·70	18·53 18·50
XVIII	180	66	$C_{12}H_9N_3O_2$ (227·2)	63·43 63·40	3·99 3·93	18·49 18·44

bacteria used. Whereas compounds *III*, *IV*, *VII*–*X*, and *XII* showed strong activities (inhibition zones from 10–80 mm) against all the bacteria used, especially against *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Micrococcus roseus*, and *Staphylococcus aureus*. Furthermore, compound *XVIII* showed the stronger antibacterial activity (inhibition zones from 35–90 mm) against all the bacteria used except *Serratia sp.*

EXPERIMENTAL

All chemicals used were reagent grade and were purified prior to use. Melting points were determined on Kofler melting point apparatus and are uncorrected. Elemental analysis was performed on Perkin–Elmer 240 E Microanalyzer. IR spectra were recorded on a Pye–Unicam SP-200 G infrared spectrophotometer, using KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM-390 MHz instrument in the suitable deuterated solvent, using TMS as internal reference. 3-Methyl-(1*H*) and/or 1,3-dimethyl-2-quinoxalinones (*I*, *II*) were prepared as reported previously[4,5].

TABLE II

Biological screening of compounds *I*–*XVIII* (inhibition zones in mm)

Compound	*Bacillus cereus*	*Serratia sp.*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Micrococcus roseus*	*Staphylococcus aureus*
I	25	–ve	20	30	25	15	15
II	–ve	–ve	15	15	–ve	–ve	15
III	50	10	60	30	30	30	45
IV	55	15	60	40	45	20	40
V	10	–ve	60	–ve	10	10	20
VI	10	–ve	65	15	–ve	–ve	25
VII	40	10	70	5	40	20	35
VIII	45	15	70	30	35	30	40
IX	50	10	70	40	25	25	30
X	55	25	75	30	50	40	45
XI	40	–ve	75	–ve	40	40	35
XII	70	25	80	20	60	35	50
XIII	20	–ve	30	–ve	10	25	30
XIV	20	–ve	30	–ve	10	–ve	10
XV	–ve	–ve	20	–ve	15	10	15
XVI	15	5	25	20	20	30	40
XVII	–ve	–ve	10	–ve	10	–ve	10
XVIII	90	35	90	80	70	80	90

Synthesis

N-(1*H*) *and/or* N-*methyl*-3-(α-*dimethylaminomethylene*-α-*formylmethyl*)-2-*quinoxalinones* (III, IV). To dimethyl formamide (6 ml) cooled to 0°C, phosphorus oxychloride was added (2·1 ml, 0·044 mol) and the mixture left to stand for 20 min. To this was added with stirring quinoxalinones *I*, *II*, respectively (2·5 g), dissolved in dimethyl formamide (15 ml). The reaction mixture was heated at 60–65°C for 5 h. The cooled reaction mixture was poured into ice-cold water and treated with $NaHCO_3$ to pH 9. The yellowish red solids (*III*, *IV* that separated out were filtered, washed with cold water and crystallized from ethanol. The physical and analytical data are given in Table I. The ^{1}H NMR spectrum of compound *III* ($CDCl_3$): 3·60 s, 6 H ($N(CH_3)_2$); 9·50 d, 1 H (acrolein-CHO, J = 3 Hz, allylic coupling); 8·50 d, 1 H (acrolein methin); 10·56 s, 1 H (NH); 8·20–7·10 m, 4 H (Ar–H). The IR spectrum: a band at 1 740 cm^{-1} (acrolein-CHO, vinylogous amide), at 3 380 cm^{-1} (NH) and at 1 710 cm^{-1} (C=O). Compound *IV*, ^{1}H NMR: 3·40 s, 3 H ($N(CH_3)_2$); 2·31 s, 3 H ($N-CH_3$); 9·25 d, 1 H (acrolein-CHO, J = 3 Hz, allylic coupling); 8·30 d, 1 H (acrolein methin); 8·10–7·20 m, 4 H (Ar-H). IR spectrum: a band at 1 730 cm^{-1} (acrolein-CHO, vinylogous amide) and at 1 690 cm^{-1} (C=O).

N-(1*H*) *and/or* N-*methyl*-3-(α-*hydroxymethylene*-α-*formylmethyl*)-2-*quinoxalinones* (V, VI). The acrolein derivative (1 g) taken in 5% aqueous sodium hydroxide (10 ml) was heated at 80°C (smell of dimethylamine) till the clear solution was obtained (30 min). It was then cooled, filtered and acidified. The solid that separated was filtered, washed and crystallized from aqueous ethanol. The ^{1}H NMR spectra in $CDCl_3$ for *V* and *VI* showed the absence of the signals due to $N(CH_3)_2$ group and the presence of all the other protons. The IR spectra of the same compounds showed the bands at 1 730–1 720 cm^{-1} (CHO), at 3 400 cm^{-1} (broad, OH), and at 1 710–1 695 cm^{-1} (C=O).

N-(1*H*) *and/or* N-*methyl*-3-(α-*piperidino or morpholino and piperazino methylene*-α-*formyl*-*methyl*)-2-*quinoxalinones* (VII–XII). To the acrolein derivatives *III*, *IV* (1 g) dissolved in ethanol (20 ml) was added an equimolar quantity of the amine and the mixture was gently heated on a water bath. The solution was evaporated to dryness and the resulting residue was crystallized from benzene, to afford the products *VII–XII*, respectively. The structures of these compounds were confirmed by their correct elemental analysis, IR and ^{1}H NMR spectra. The ^{1}H NMR spectrum of *VII* in $CDCl_3$ showed signals at δ 3·56 and δ 3·47 due to the piperidine ring (–N–CH_2–). The IR spectrum indicated the presence of CHO group at 1 730–1 720 cm^{-1}, C=O group at 1 695 cm^{-1} and NH group at 3 280 cm^{-1}.

N-(1*H*) *and/or* N-*methyl*-3-(4-*isoxazolyl or pyrazolyl*)-2-*quinoxalinones* XIII–XVIII. To a solution of acrolein derivatives *III*, *IV* in ethanol (20 ml) was added an equimolar quantity of hydroxylamine hydrochloride, hydrazine hydrate or phenyl hydrazine, respectively. The reaction mixture was refluxed for 2 h, cooled, concentrated and poured onto crushed ice. The precipitated coloured solid was filtered off, washed thoroughly with water and crystallized from aqueous ethanol. ^{1}H NMR spectra which indicate the absence of the signals related to $N(CH_3)_2$ or CHO groups and the presence of signals at δ 10·30 (NH) which were removed by D_2O(compounds *XIII–XV* and *XVI*), along with the signals for all the other protons. The IR spectra showed the absence of a band related to CHO group and the presence of bands at 3 230–3 210 cm^{-1} (NH), 1 630–1 610 cm^{-1} (C=N), and at 1 720 cm^{-1} (C=O).

Biological Activity

The antibacterial activities of all synthesized compounds against *Bacillus cereus*, *Serratia sp.*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Micrococcus roseus* and *Staphylo-*

coccus aureus were tested by the usual cup plate agar diffusion technique[6–8], 1% (w/w) solutions of these compounds were prepared. The dishes were allowed to stand in a refrigerator at 4—8°C for 0·5 h, to allow diffusion of the solutions and they were then incubated at 37 ± 1°C for 48 h. The inhibition zones were measured with the callipers. The results are presented in Table II.

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