SYNTHESIS OF SOME PYRAZINO-1,4-BENZOXAZINES AND 1,4-OXAZINO BENZODIAZEPINES

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ABSTRACT

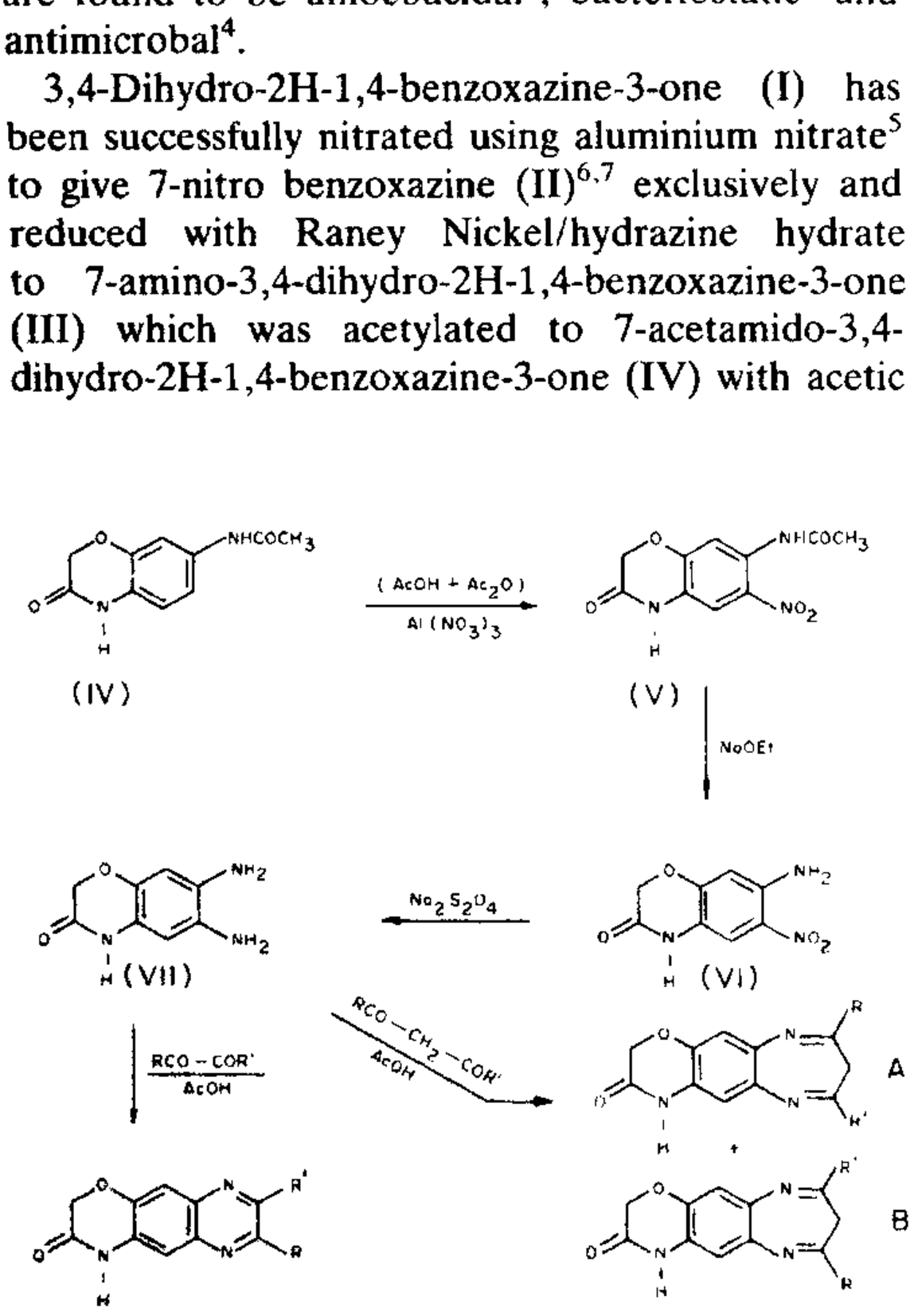
Various 7,8-diphenyl-2H-pyrazino[2,3-g]-1,4-benzoxazine-3(4H)-ones (IX) and 4,8-dihydro-7,9-dimethyl and 7,9-diphenyl-1,4-oxazino [2,3-h][1,5]benzodiazepines-3(2H)-ones (VIII) and 7-acetamido-6-nitro (V), 7-amino-6-nitro (VI) and 6,7-diamino-2H-1,4-benzoxazine-3-one (VII) are being reported for the first time. The title compounds have been screened for their antibacterial activity.

INTRODUCTION

EXHAUSTIVE survey of literature revealed that no attempt has been made to nitrate 2H-1,4-benzoxazine-3-one or much less to build up any heterocyclic appendages. The present paper reports the synthesis of the title compounds and reports their biological potency. Benzodiazepines are cancerostatics[1], quinoxalines and their N,N-dioxides are found to be amoebacidal[2], bacteriostatic[3] and antimicrobal[4].

3,4-Dihydro-2H-1,4-benzoxazine-3-one (I) has been successfully nitrated using aluminium nitrate[5] to give 7-nitro benzoxazine (II)[6,7] exclusively and reduced with Raney Nickel/hydrazine hydrate to 7-amino-3,4-dihydro-2H-1,4-benzoxazine-3-one (III) which was acetylated to 7-acetamido-3,4-dihydro-2H-1,4-benzoxazine-3-one (IV) with acetic anhydride to facilitate further nitration. 7-Acetamido-3,4-dihydro-2H-1,4-benzoxazine-3-one (IV) was nitrated using aluminium nitrate[5] in a mixture of 2:3 acetic acid and acetic anhydride giving exclusively 6-nitro isomer (V) which was characterized by PMR spectra. Hydrolysis and then reduction with sodium dithionite gave 6,7-diamino-3,4-dihydro-2H-1,4-benzoxazine-3-one (VIII).

In the present work diazepines and pyrazines were obtained by refluxing 6,7-diamine with 1,2 and 1,3-dicarbonyl compounds in boiling DMSO and acetic acid. Reaction of diamine with unsymmetrical 1,3-dicarbonyl compounds yielded a compound which on passing through a column of silica gel afforded two crystalline compounds A from benzene fraction and B from 9:1 benzene : ethyl acetate mixture. Both the compounds gave identical PMR spectra. In TLC the R_f values were 0.42 and 0.40 respectively.



EXPERIMENTAL

All melting points were taken in open capillaries and were uncorrected. The IR spectra were recorded on Perkin–Elmer spectrometer and the PMR spectra on 100 MHz spectrometer using TMS as internal standard.

7-Acetamido-6-nitro-2H-1,4-benzoxazine-3(4H)-one (V):

7-Acetamido benzoxazine (0.05 mol) was dissolved in a mixture of 20 ml of acetic acid and 30 ml acetic anhydride. Finely powdered aluminium nitrate (0.07 mol) was added in small lots maintaining the temperature at 20°C to 25°C and then stirred for 1 hr and diluted with crushed ice, filtered and purified from ethanol and characterized by IR and

PMR. M.P. 272°C yielded 95%. Found: N, 16.68%, $C_{10}H_9N_3O_5$ requires N, 16.74%.

$IR_{\nu\ max}$ KBr cm^{-1}:	3375 (NH-CO-CH_3 and NH-CO)
	1685 (NH-CO)
	1645 (NH-CO-CH_3)
PMR (DMSO-d_6)δ:	2.15 (s, 3H, NH-COCH_3)
	4.76(s, 2H, CH_2)
	7.46 (s, 1H, C_5 Ar-H)
	7.6 (s, 1H C_8 Ar-H)
	10.18 (b, 1H, NH-CO-CH_2)
	10.94 (b, 1H, NH-CO-CH_3)

7-Amino-6-nitro-2H-1, 4-benzoxazine-3(4H)-one (VI):

7-Acetamido-6-nitro-2H-1,4-benzoxazine-3(4H)-one (0.05 mol) was hydrolyzed with 200 ml of 5% ethanolic KOH under reflux for 30 min and diluted with crushed ice, neutralized with dilute HCl. The resulting solid was recrystallized from methanol. M.P. 295°C (decomp) yield 90%. Found: N, 19.59%, $C_8H_7N_3O_4$ requires N, 19.71%.

$IR_{\nu\ max}$ KBr cm^{-1}:	3480–3340 (d, NH_2)
	1675 (NH-CO-CH_2)
PMR (DMSO-d_6)δ:	4.68 (s, 2H, CH_2)
	6.55 (s, 1H, C_5Ar-H)
	7.54 (s, 1H, C_8Ar-H)
	7.38 (b, 2H, NH_2)
	10.72 (b, 1H, NH-CO)

6,7-Diamino-2H-1,4-benzoxazine-3(4H)-one (VII):

7-Amino-6-nitro-2H-1, 4-benzoxazine-3(4H)- one (0.05 mol) was dissolved in excess boiling aqueous alcohol and 60 g of sodium dithionite added in small lots. The solution became colourless and added to crushed ice to give white flakes of diamine which was filtered and reprecipitated from acetic acid. M.P. 262°C, yield 70%. Found: N, 21.39%, requires $C_8H_9N_3O_2$, N, 21.31%.

$IR_{\nu\ max}$ KBr cm^{-1}:	3350–3200 (sharp doublet–NH_2, NH_2)
	1655 (NHCO-CH_2)
PMR (DMSO-d_6)δ:	3.96–4.32 (b, 2H, CH_2, 4H, NH_2 and NH_2 merged broad peak)
	6.20 (s, 1H, C_5Ar-H)
	6.28 (s, 1H, C_8Ar-H)

4,8-Dihydro-7,9-dimethyl-1,4-oxazino[2,3-h][1,5] benzodiazepine-3(2H)-one (VIII):

To 6,7-diamino-2H-1,4-benzoxazine-3(4H)-one (0.01 mol) dissolved in 20 ml glacial acetic acid (0.012 mol) distilled acetylacetone was added and refluxed for 2 hr, poured into crushed ice. The solid was filtered and recrystallized from $CHCl_3$ methanol mixture. M.P. 332°C (decomp), yield 85%. Reaction was also carried out in DMSO 15 ml and diluted with water.

$IR_{\nu\ max}$ KBr cm^{-1}:	3140–2960 (b, CH_3, CH_3 and CH_2)
	1685 (NH-CO-CH_2)
PMR (DMSO-d_6)δ:	4.52 (s, 2H, CH_2)
	2.4–2.55 (m, 8H, CH_3, CH_3 and CH_2)
	7.0–7.08 (d, J = 4 Hz, 2H, ArH)
	10.61 (b, 1H, NH-CO).
VIII e(A)	R = 2-Hydroxyphenyl
	R′ = Phenyl
e(B)	R = Phenyl
	R′ = 2-hydroxyphenyl
$IR_{\nu\ max}$ KBr cm^{-1}:	3270–3090 (b, oxazine NH)
	1670 (NH-CO-CH_2)
PMR (DMSO-d_6)δ:	1.61 (s, 2H, CH_2 diazepine)
	4.49 (s, 2H, CH_2 oxazine)
	7.12–7.90 (m, 11H, Ar-H)
	9.34 (b, 1H, Ar-OH)
	10.44 (b, 1H, NH-CO)

7,8-Diphenyl-2H-pyrazino[2,3-g]-1,4-benzoxazine-3(4H)-one (IX):

To diamine (VII) (0.01 mol) dissolved in 15 ml of dimethyl sulphoxide (0.014 mol), benzil was added and refluxed for 30 min. The solution was poured into crushed ice to give the title compound which was filtered and purified from benzene and methanol mixture to give fine needles. M.P. 294°C, yield 80%. Reaction was also carried out in glacial acetic acid (20 ml).

$IR_{\nu\ max}$ KBr cm^{-1}:	3160–2840 (C=C, C=N
	1700 (NH-CO)
PMR (DMSO-d_6)δ:	4.82 (s, 2H, CH_2)
	7.41–7.56 (m, 12H, ArH)
	11.42 (b, 1H, NH)

Table 1 *Oxazino benzodiazepines*

Sl No.	R	R′	Mol. formula	m.p. °C	% Nitrogen Found	% Nitrogen Calcd
VIII a	CH_3	CH_3	$C_{13}H_{13}N_2O_2$	332	12.13	12.22
b	C_6H_5	C_6H_5	$C_{23}H_{27}N_3O_2$	345	11.41	11.44
c	2-Hydroxy phenyl or 4-Methoxy phenyl	4-Methoxy phenyl or 2-Hydroxy phenyl	$C_{24}H_{19}N_3O_4$	99	10.18	10.16
			$C_{24}H_{19}N_3O_4$	189	10.18	10.16
d	2-Hydroxy phenyl or 4-Nitro phenyl	4-Nitro phenyl or 2-Hydroxy phenyl	$C_{23}H_{16}N_4O_5$	280	12.97	13.08
			$C_{23}H_{16}N_4O_5$	330	12.97	13.08
e	2-Hydroxy phenyl or Phenyl	Phenyl or 2-Hydroxy phenyl	$C_{23}H_{17}N_3O_3$	236	10.87	10.95
			$C_{23}H_{17}N_3O_3$	294	10.87	10.95
f	4-Methoxy phenyl	4-Methoxy phenyl	$C_{25}H_{21}N_3O_4$	291	10.51	10.58

Table 2 *Pyrazino benzoxazines*

Sl No.	R	R′	Mol. formula	m.p. °C	% Nitrogen Found	% Nitrogen Calcd
IX a	H	H	$C_{10}H_7N_3O_2$	300	20.71	20.89
b	CH_3	CH_3	$C_{12}H_{11}N_3O_2$	320	18.22	18.34
c	Phenyl	Phenyl	$C_{22}H_{15}N_3O_2$	291	11.61	11.89
d	4-Chloro phenyl	4-Chloro phenyl	$C_{22}H_{13}Cl_2N_3O_2$	286	10.10	9.97
e	4-Methyl phenyl	4-Methyl phenyl	$C_{24}H_{19}N_3O_2$	272	11.02	11.02
f	4-Methoxy phenyl	4-Methoxy phenyl	$C_{24}H_{19}N_3O_4$	312	10.12	10.16
g	4-Nitro phenyl	4-Nitro phenyl	$C_{22}H_{13}N_5O_6$	286	15.76	15.80
h	Furyl	Furyl	$C_{18}H_{13}N_3O_4$	252	12.39	12.51

Satisfactory analysis for C and H were obtained. Yields ranged from 70% to 90%. Recrystallization of pyrazines from methanol and benzodiazepines from methanol and chloroform 1:2 mixture.

Anti-bacterial activity: The anti-bacterial activity of compounds (VIII) and (IX) was evaluated against *Bacillus subtilis* and *Staphylococus aureas* using the agar diffusion technique[8] and the plates were incubated at 37°C for 24 hr. Tetracycline hydrochloride was used as control against both microorganisms. All the test compounds (VIII) and (IX) in table 1 and 2 exhibited any significant inhibition of growth of activity.

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Topics covered at the Symposium are as follows: 1. Nutritional Physiology and Metabolism, 2. Osmoregulation and Respiration, 3. Sensory, Effector and Neuroendocrine Physiology, 4. Physiology of Reproduction, and 5. Environmental Physiology and Toxicology.

The last date for receipt of abstracts is *December 31, 1986.*

For further particulars please contact: The Secretary, Dr (Mrs.) R. Sarojini, Reader in Crustacean Endocrinology, Department of Zoology, Marathwada University, Aurangabad 431 004.