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STUDIES ON 1,4-BENZOXAZINES—I

PREPARATION, STRUCTURE, REACTIONS AND SPECTRAL DATA OF SOME 2*H*-1,4-BENZOXAZIN-3-THIONES

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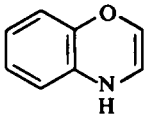
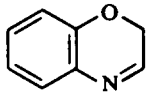
Abstract—Several 2*H*-1,4-benzoxazin-3-thiones have been newly prepared. UV, IR and NMR studies establish that the predominant tautomer in these potentially tautomeric compounds is the thiolactam form. Methylation gives the S-Me and not the N-Me derivative. NMR spectroscopy is useful in distinguishing between isomeric benoxazine structures and between exocyclic and endocyclic double bonds in the hetero ring. Nucleophilic displacement reactions have been carried out on 2*H*-1,4-benzoxazin-3-thione and its S-Me and N-Me derivatives using hydrazine hydrate, morpholine, cyclohexylamine and aniline. In each case NMR has been used to ascertain the structure of the reaction product.

BENZOXAZINES, of which eight isomers are theoretically possible,[1] have been a rather meagrely explored class of heterocyclic compounds. In many cases even the parent members are unknown. So far the most widely studied isomers are those derived from 1,3-oxazine, namely, 1,3-4*H*-, 1,3-4*H* and 3,1-4*H*-benzoxazines, the interest having stemmed from the discovery of antitubercular activity[2] in several members of this series. Anticancer activity has also been reported for some compounds of this series.[3]



I



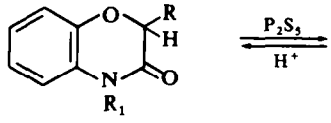
II

There are two possible isomers (I and II) of 1,4-benzoxazine. By virtue of their tautomeric nature these two forms are generally regarded as inseparable. Neither the parent member nor any of its simple substituted derivatives has been prepared. The majority of the compounds known in the literature are derivatives of 2*H*-1,4-benzoxazin-3-one* (III), the most easily accessible member of this class. The present report deals with the preparation, tautomeric structures, some reactions and spectral properties of 2*H*-1,4-benzoxazin-3-thiones.

Preparation. The most obvious route to 2*H*-1,4-benzoxazin-3-thiones appeared to be by reaction of phosphorus pentasulphide with the corresponding oxo compounds for which lactam form III is evidently the preferred structure. Treatment of 2*H*-1,4-benzoxazin-3-one (III) or its 2-Me derivative (IV) with P_2S_5 in refluxing xylene (or

* This nomenclature will be used in this paper. Other names found in literature are: 3-phenmorpholone, 3-ketophenmorpholine, 3-hydroxy-1,4-benzoxazine.

pyridine, lower yields) gave excellent yields of 2*H*-1,4-benzoxazin-3-thione (VII) and 2-methyl-2*H*-1,4-benzoxazin-3-thione (VIII) respectively. The thio compounds were soluble in dilute aqueous alkali and could be reprecipitated by acid. Both VII and VIII were stable in 5% hydrochloric acid even on prolonged contact at room temperature but heating with 1:1 aqueous hydrochloric acid or 50% chloroacetic acid solution at 90° for 6 hr converted them back to the corresponding oxo compounds III and IV respectively.

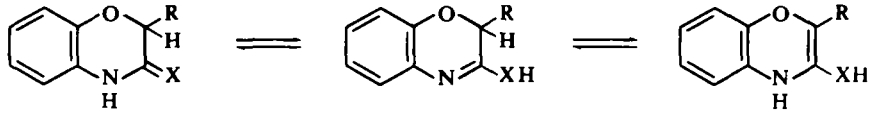


III: R = R_1 = H
IV: R = CH_3; R_1 = H
V: R = H; R_1 = CH_3
VU: R = R_1 = CH_3

VII: R = R_1 = H
VII: R = CH_3; R_1 = H
IX: R = H; R_1 = CH_3
X: R = R_1 = CH_3

Methylation of VII or VIII gave exclusively the corresponding S-Me derivatives, 3-methylthio-2*H*-1,4-benzoxazine (XI) and 3-methylthio-2-methyl-2*H*-1,4-benzoxazine (XII) respectively. For comparison the corresponding N-methylated analogues, namely, N-methyl-2*H*-1,4-benzoxazin-3-thione (IX) and 2,4-dimethyl-2*H*-1,4-benzoxazin-3-thione (X) were prepared by the action of P_2S_5 on N-methyl-2*H*-1,4-benzoxazin-3-one (V) and 2,4-dimethyl-2*H*-1,4-benzoxazin-3-one (VI) respectively. The physical properties of XI and XII were different from those of the N-Me derivatives IX and X. The NMR spectral data summarized in Table 1 provided further proof of structure assigned for the S-methylated products. Although a tautomeric structure (XIa) can be visualized for the S-methylated product XI, this is ruled out by NMR on the basis of the presence of a singlet for C_2 methylene protons and absence of absorption for vinylic, and N*H* protons. The pattern of UV absorption of XI is also different from that of VII and IX (Fig. 1). Likewise, the presence of a methine quartet and absence of NH in the NMR spectrum rules out structure XIIa, the tautomeric possibility for XII.

Tautomeric structures. The study of prototropic movements leading to lactim–lactam tautomerism in heterocyclic systems has recently received considerable attention. Earlier, UV, IR and basicity measurements were extensively employed to study this problem but the advent of NMR spectroscopy has enabled a better probe into this question. Compounds encountered by earlier workers have been mainly potential lactim–lactam tautomers (where the mobile H atom can wander from the ring N to the adjacent hetero atom such as O, S or N) or keto–enol tautomers. Examples



III: R = H; X = O
VII: R = H; X = S
VIII: R = CH_3; X = S

IIIa
VIIa
VIIIa

IIIb
VIIb
VIIIb

TABLE 1. PROTON CHEMICAL SHIFT DATA OF 2*H*-1,4-BENZOXAZINE DERIVATIVES

Compound	—O<u>CH</u>$_2$ or —OCHR—	NC<u>H</u>$_3$	N<u>H</u>	Aromatics
III	4·52 s	—	10·60[b]	6·90 s
IV	R 1·58 d H 4·66 q	—	8·87[b]	6·95 s
V	4·60 s	3·55 s	—	7·02 s
VI	R 1·50 d H 4·57 q	3·50 s	—	6·93 s
VII	4·80 s	—	10·90[b]	7·00 s
VIII	R 1·70 d H 5·08 q	—	—	7·05 s
IX	4·88 s	3·83 s	—	7·07 s
X	R 1·50 d H 5·07 q	3·80 s SC<u>H</u>$_3$	—	7·03 s
XI	4·50 s	2·55 s	—	7·00 m
XII	R 1·43 d H 4·55 q	2·47 s	—	7·00 m
XIII[b]	4·57 s	—	9·43[b]	6·90 m
XIV	5·2 s	3·4 s	—	6·95 s
XV	4·67 s	—	—	6·97 m 3·52 m (4)[c] 3·83 m (4)[d]
XVI	4·40 s	—	5·08[b]	7·08 m 4·00 m (1)[e] 1·65 m (10)[f]
XVII	4·57 s	—	7·1[b]	6·90 s (4)[g] 7·30 s (5)[h]

Abbreviations: s = singlet, d = doublet, q = quartet, m = multiplet, b = broad.

[a] Chemical shifts are referred to in δ units (parts per million) relative to TMS, $\delta = 0$. In all cases integral data support the assignments. Unless otherwise indicated spectra were obtained for deuterochloroform solutions. Figure in paranthesis refers to proton count.

[b] In 6D-DMSO solution.

[c] Assigned to the two methylenes linked to morpholine nitrogen.

[d] Assigned to the two methylenes linked to morpholine oxygen.

[e] Assigned to the methine proton on the cyclohexyl ring.

[f] Methylene protons of the cyclohexyl moiety.

[g] Aromatic protons of the benzoxazine nucleus.

[h] Aromatic protons of the aniline moiety.

involving both lactim–lactam tautomerism and keto–enol tautomerism in the same structure are not very common. The present series of benzoxazine derivatives offered suitable models for this study.

The three tautomeric structures conceivable for 2*H*-1,4-benzoxazin-3-thione (VII) are represented by VII, VIIa and VIIb. Similar structures can be written for 2*H*-1,4-benzoxazin-3-one (III, IIIa and IIIb). The predominent tautomer became evident from a study of their UV, IR and NMR spectra.

UV spectra. The UV spectral data of several of 3-oxo-, 3-thio-, 3-methylthio- and 3-amino substituted-1,4-benzoxazines presented in Table 2 show that the 3-thiones (VII, VIII, IX and X) exhibit an absorption pattern very similar to that of the corresponding oxo compounds (III, IV, V and VI) but different from the S-Me

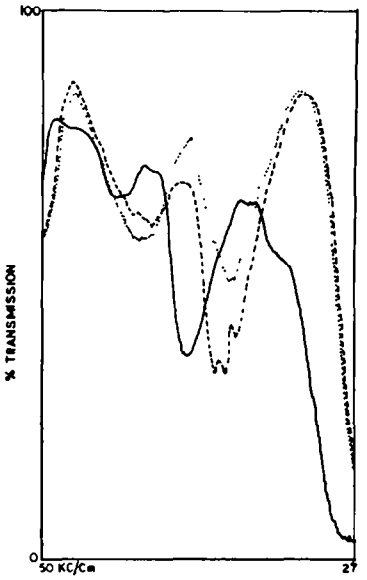


FIG. 1. UV spectra of: 2*H*-1,4-benzoxazin-3-thione, VII (– – – –); N-Methyl-2*H*-1,4-benzoxazin-3-thione, IX (. . . . .); and 3-Methylthio-2*H*-1,4-benzoxazine, XI (———).

compounds (XI and XII) suggesting thereby that there is no contribution from the enol form in 2*H*-1,4-benzoxazin-3-thiones, although methylation gives the corresponding S-Me and not the N-Me derivative. The bathochromic shift in absorption maxima in going from the oxo to the corresponding thio compounds is expected of auxochrome sulphur, as also observed earlier.[4]

IR spectra. Sullivan and Sadler[5] studied the IR absorption of 2*H*-1,4-benzoxazin-3-one (III) in solid and solution states. Based on the carbonyl absorption in the 1700 cm^{-1} region and NH absorption around 3200 cm^{-1} in solid state (3400 cm^{-1} in soln) they supported the lactam structure. The important IR absorption bands in the present series of 2*H*-1,4-benzoxazin-3-thiones presented in Table 2 reveals the predominent tautomer. All the compounds exhibit a strong thiocarbonyl (C═S) absorption in the interval 1100 and 1150 cm^{-1}. This is in agreement with reports[6, 7, *] indicating 1150 $\pm$ 70 cm^{-1} as the region for thiocarbonyl absorption.

Compounds VII and VIII exhibit a medium absorption between 3000–3200 cm^{-1} indicating the presence of an H-bonded secondary NH group. For dilute solutions this absorption appears at 3410–3420 cm^{-1} as in the corresponding 3-oxo compounds [2*H*-1,4-benzoxazin-3-one, VII, 3140 (KBr), 3360 cm^{-1} ($CHCl_3$); 2-methyl-1,4-benzoxazin-3-one, VIII, 3130 (KBr), 3345 cm^{-1} ($CHCl_3$)]. The lower m.p. of IX (78°) as compared to VII (121°) suggests intermolecular H-bonding of the NH in VII.

These data and the absence of any absorption in the SH region adduce support to the view that the 2*H*-1,4-benzoxazin-3-thiones exist in the solid and liquid states mainly in their unsaturated thio lactam forms.

NMR spectra. The NMR spectra of all the 2*H*-1,4-benzoxazin-3-thiones described

* E. Spinner[8] assigns the region around 1140 cm^{-1} for C═S absorption.

TABLE 2. UV AND IR DATA OF 2*H*-1,4-BENZOXAZINE DERIVATIVES

Compound	UV[a] max mμ (log E)				IR cm^{-1}		
					NH stretching		C=O stretching
					in $CHCl_3$	in KBr	
Oxo compounds							
2*H*-1,4-benzoxazin-3-one (III)	256·4	(3·66)	282·5	(3·42)	3360 m	3140 m	1695 s
2-Methyl-2*H*-1,4-benzoxazin-3-one (IV)	254·6	(3·86)	282·0	(3·74)	3345 m	3130 m	1680 s
N-Methyl-2*H*-1,4-benzoxazin-3-one (V)	256·4	(3·79)	283·0	(3·63)	—	—	1675 s
2,4-Dimethyl-2*H*-1,4-benzoxazin-3-one (VI)	254·5	(3·90)	281·5	(3·78)	—	—	1670 s
Thio compounds							C = S
2*H*-1,4-benzoxazin-3-thione (VII)	252·5	(3·97)	322·5	(4·07)	3420 m	3170 m	1125 s
	278·0	(3·56)					
2-Methyl-2*H*-1,4-benzoxazin-3-thione (VIII)	252·0	(4·08)	326·8	(4·25)	3410 m	3165 m	1140 s
N-Methyl-2*H*-1,4-benzoxazin-3-thione (IX)	256·0	(4·00)	322·5	(4·02)	—	—	1120 s
2,4-Dimethyl-2*H*-1,4-benzoxazin-3-thione (X)	252·0	(4·10)	324·5	(4·20)	—	—	1135
3-Methylthio-2*H*-1,4-benzoxazine (XI)	238·0	(4·10)	292·5	i(4·03)			
	284·0	(4·02)	308·5	(3·90)			
3-Methylthio-2-methyl-2*H*-1,4-benzoxazine (XII)	237·5	(4·15)	293·0	(4·10)			
	283·5	(4·05)	308·0	(3·88)			

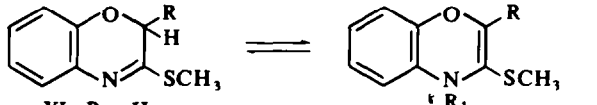
Abbreviations: m = medium, s = strong, i = inflexion.

[a] Taken in 95% ethanol.

in this paper have been examined to confirm structure and also to establish the predominant tautomer in the potentially tautomeric systems. The spectral data presented in Table 1 permit certain generalizations to be drawn.

The C_2 methylene protons. The presence of a sharp singlet integrating to two protons in the region 4·5–5 in all three potentially tautomeric oxo and thio compounds (III–X) fixes the C_2-methylene protons and eliminates the possibility of a methylene hydrogen participating in keto–enol tautomerism. The deshielding effect of thiocarbonyl group on the C_2-methylenes is more (0·4–0·6 ppm) than of the simple CO group. This may be due to the larger size of the S atom resulting in shorter distance of the methylenes from the outermost orbit of sulphur. 2-Methyl-3-oxo (IV) and 2-methyl-3-thio (VIII) analogs of 2*H*-1,4-benzoxazine furnish additional proof for the non-involvement of the C_2-methylene proton in enolization. If the hydrogen at C_2 is involved in tautomerism a singlet should appear for the C_2-Me group in IV and VIII and the mobile C_2 hydrogen should give a peak in the OH or SH region as the case may be. However, in both IV and VIII the pattern observed is a doublet for the C_2-Me and a quartet for the C_2-proton, thereby ruling out the possibility of enolic structures for the oxo and thio compounds (III–X).

The aromatic pattern. The four aromatic protons of 2*H*-1,4-benzoxazin-3-one (III), its thio analogue (VII) and their 2-Me and N-Me derivatives (IV, V, VI, VIII, IX and X) appear invariably as a *singlet* around 7·00 (Table 1), indicating that the four aromatic protons in the respective compounds are magnetically equivalent. In the S-methylated compounds (XI and XII) the pattern is distinctly different, the four aromatic protons appearing as a *multiplet* around 7·00. This shows that the endocyclic double bond created by S-methylation disturbs the magnetic equivalence of all the four aromatic protons. This effect has helped distinguish an endocyclic double bond (XI and XII) from an exocyclic double bond (II–X) in this series of compounds.



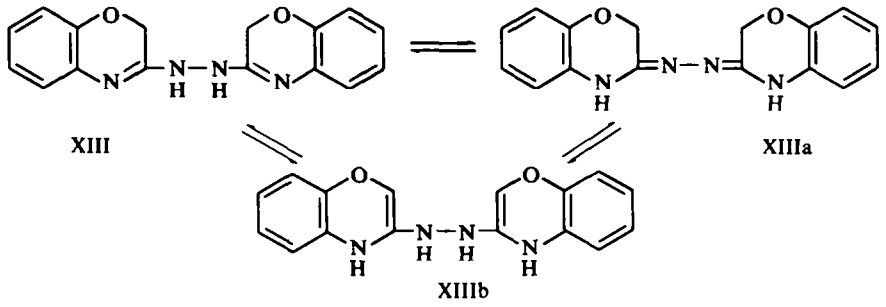
XI: R = H
XII: R = CH_3

XIa: R = R_1 = H
XIIa: R = CH_3; R_1 = H

Reactions of 2H-1,4-*benzoxazin*-3-*thione*

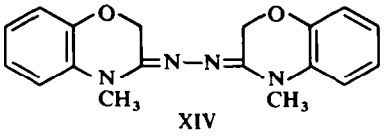
A thio or methylthio group in heterocyclic compounds is known to undergo facile replacement by amino groups.[9] With a view to getting new compounds for pharmacological evaluation, 2*H*-1,4-benzoxazin-3-thione (VII) was reacted with hydrazine hydrate, cyclohexylamine, aniline, and morpholine. Assignment of structure to the product in each of these cases utilized the distinction in aromatic pattern in the NMR (discussed earlier) as a diagnostic tool.

The reaction of 2*H*-1,4-benzoxazin-3-thione (VII) or its S-Me derivative (XI) with hydrazine hydrate gave a product for which three tautomeric structures (XIIIa–c) are possible. NMR showed a singlet at 4·57 assignable to the C_2-methylene protons and this ruled out the structure XIIIb. A multiplet observed for the four aromatic protons favoured, on the basis of previous analogy, structure XIII. A similar reaction of hydrazine hydrate on N-methyl-2*H*-1,4-benzoxazin-3-thione (IX) also produced a bis product, the NMR spectrum of which showed a singlet for N–Me

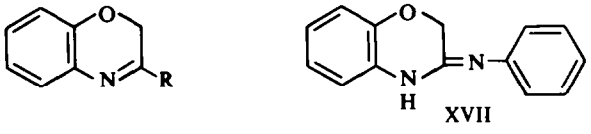


XIII XIIIa XIIIb

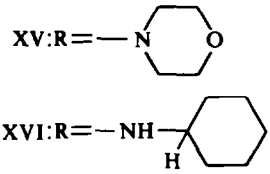
protons, a singlet (2H) at 5·20 assignable to the C_2-methylene protons and a singlet for the four aromatic protons. The bis product was assigned structure XIV. On a similar basis, the product from reaction of VII with morpholine was assigned structure XV. Reaction of VII with cyclohexylamine afforded a product identified by NMR as 3-cyclohexylamino-2*H*-1,4-benzoxazine (XVI).



XIV



XVII



XV:R=

XVI:R=

On the contrary, replacement of the thio group in VII by aniline gave a product for which NMR favoured structure XVII. A singlet at 7·30 integrating for five protons accounted for the aromatic protons of the aniline moiety while another singlet at 6·90 (4H) represented the four aromatic protons of the benzoxazine ring. The broad N*H* absorption around 7·10 could be exchanged out by D_2O. These examples serve to illustrate that the pattern of aromatic absorption offers a quick method of distinguishing between 1,4-benzoxazine structures with endocyclic and exocyclic double bonds.

EXPERIMENTAL

All m.ps, taken in capillary tubes, are uncorrected. UV spectra were determined with a Unichem SP-700 recording spectrophotometer and IR spectra with a Perkin–Elmer model 221 instrument equipped with NaCl optics. NMR spectra were recorded on a Varian A-60A spectrometer.

Preparation of 2H-1,4-*benzoxazin*-3-*thiones* (Only a typical experiment is reported here).

2H-1,4-*Benzoxazin*-3-*thione* (VII). Compound III,[10] (0·1 M) was mixed with powdered P_2S_5 (0·12M) in dry xylene (300 ml) and heated under reflux for 4 hr. The mixture was cooled to room temp, filtered and washed with the same solvent (2 × 25 ml). Concentration of the filtrate under reduced press gave a viscous residue which solidified upon addition of crushed ice. The crude thio compound was purified by dissolving in 5% NaOH aq (activated carbon) and reprecipitation by dilute acid. Compound VII crystallized from pet. ether as colourless needles, m.p. 120–121°; yield 80%. (Found: C, 58·14; H, 4·35; N, 8·30; S, 19·36. C_8H_7NOS requires: C, 58·18; H, 4·27; N, 8·48; S, 19·41%).

Similarly prepared were:

2-*Methyl*-2H-1,4-*benzoxazin*-3-*thione* (VIII) from 2-methyl-2*H*-1,4-benzoxazin-3-one,[11] 90% yield; pale yellow needles from pet. ether, m.p. 129°. (Found: C, 60·17; H, 5·03; N, 7·76; S, 17·79. C_9H_9NOS requires: C, 60·30; H, 5·06; N, 78·2; S, 17·89%).

N-*Methyl*-2H-1,4-*benzoxazin*-3-*thione* was prepared from N-Methyl-2*H*-1,4-benzoxazin-3-one[11] in 85% yield, m.p. 78°. (Found: C, 59·98; H, 5·01; N, 7·69; S, 17·81. C_9H_9NOS requires: C, 60·30; H, 5·06; N, 7·82; S, 17·89%).

2,4-*Dimethyl*-2H-1,4-*benzoxazin*-3-*thione* (X) prepared from 2,4-dimethyl-2*H*-1,4-benzoxazin-3-one was purified by distillation under reduced press as a pale yellow viscous oil, b.p. 180°/2 mm; yield 75%. (Found: C, 62·31; H, 5·63; N, 7·33; S, 16·45. $C_{10}H_{11}NOS$ requires: C, 62·16; H, 5·74; N, 7·25; S, 16·6%).

Acid hydrolysis of 2H-1,4-*benzoxazin*-3-*thiones*

The 3-thione (0·1M) was converted into the corresponding 3-oxo compound when heated with 1:1 HCl aq (75 ml) or aqueous chloroacetic acid (25%, 100 ml) on a steam bath for 6 hr. The product was isolated by pouring into cold water (100 ml).

3-*Methylthio*-2H-1,4-*benzoxazine* (XI)

(a) *With methyl iodide in acetone.* To VII (8·25 g, 0·05M) dissolved in warm acetone (100 ml) containing powdered KOH (7 g) was added MeI (11 g; 0·075 mole) in two portions at an interval of 15 min. The mixture was then refluxed for 2 hr, cooled and filtered to remove KI. Concentration of the filtrate under reduced press gave the crude XI as a pale yellow oil which was purified by distillation, b.p. 130–132°/4 mm; yield, 90%. (Found: C, 60·15; H, 5·02; N, 7·65; S, 17·63. C_9H_9NOS requires: C, 60·30; H, 5·06; N, 7·82; S, 17·89%).

(b) *By methyl iodide in aqueous alkali.* MeI (11 g) was added dropwise to a stirred solution of VII (8·25 g) in 1N KOH (200 ml) at room temp. The oily product was extracted with ether, dried (Na_2SO_4), concentrated and finally fractionated under reduced press to give XI b.p. 120–124°/2 mm; yield (75%). IR spectra, TLC identical with that of product obtained by Method A.

3-*Methylthio*-2-*methyl*-2H-1,4-*benzoxazine* (XII) was prepared in 80% yield by Method A and 65% yield by Method B, b.p. 120°/3 mm. (Found: C, 62·23; H, 5·67; N, 7·29; S, 16·75. $C_{10}H_{11}NOS$ requires: C, 62·16; H, 5·74; N, 7·25; S, 16·6%).

1,2-*bis*[3-(2H-1,4-*benzoxazinyl*)]*hydrazine* (XIII)

Method A. Compound VII, (3·3 g; 0·02M) was heated with hydrazine hydrate (10 ml) in abs EtOH (75 ml) under reflux for 3 hr. The soln was concentrated to a small bulk and poured on crused ice to give XIII, m.p. 208°; yield (40%) needles from pet ether–benzene). (Found: C, 65·27; H, 4·65; N, 19·13. $C_{16}H_{14}N_4O_2$ requires: C, 65·30; H, 4·79; N, 19·04%).

Method B. Compound XIII was obtained in 45% yield from XI (3·58 g), hydrazine hydrate (2 g) and EtOH or dioxan (50 ml) adopting the experimental procedure of Method A.

1,2-*bis*[3-(2H-1,4-*benzoxazinylidene*)]*hydrazine* (XIV)

Compound IX (0·1M) was heated with excess hydrazine hydrate (0·4M) on a sand bath at 100° for 3 hr. Excess hydrazine hydrate was removed under reduced press and the residue was triturated with crushed ice to give XIV as a light green solid which was crystallized from benzene–pet ether as colourless needles, m.p. 211°; yield 38%. (Found: C, 67·37; H, 5·15; N, 17·39 $C_{18}H_{16}N_4O_2$ requires: C, 67·48; H, 5·03; N, 17·49%).

3-(4′-*Morpholino*)-2H-1,4-*benzoxazine* (XV)

Compound VII (7·45 g; 0·05M) was heated with morpholine (8·3 g, 0·1M) in an oil bath for 3 hr. Excess morpholine was removed under reduced press leaving a brownish solid which crystallized from pet ether

as shining needles m.p. 114°; yield, 80%. (Found: C, 66·13; H, 6·43; N, 12·79. $C_{12}H_{10}N_2O_2$ requires: C, 66·03; H, 6·47; N, 12·84%).

3-(N-*Cyclohexylamino*)-2H-1,4-*benzoxazine* (XVI)

Compound XI (7·45 g; 0·05 M) was mixed with excess cyclohexylamine (9·8 g; 0·1 M) and heated in an oil bath at 130° for 3 hr. After removing excess cyclohexylamine under reduced press, the residue was poured on crushed ice. The resultant sticky mass was extracted in ether and washed with water (3 × 25 ml). Concentration of dried ethereal extract gave the crude XVI (75% yield) which was crystallized from pet ether as light brown crystals, m.p. 108°. An analytical sample was prepared by three crystallizations. (Found: C, 72·97; H, 7·69; N, 12·13. $C_{14}H_{18}N_2O$ requires: C, 73·01; H, 7·88; N, 12·16%).

3-*Anilino*-2H-1,4-*benzoxazine* (XVII). 7·45 g (0·05M) of VII was heated with 9·2 g (0·1M) of redistilled aniline in an oil bath at 110° for 4 hr. Removal of excess aniline and trituration of the residue with crushed ice left a brownish solid which upon recrystallization from benzene–pet ether afforded light brown needles m.p. 105°; yield, 65%. (Found: C, 74·79; H, 5·44; N, 12·43; $C_{14}H_{12}N_2O$ requires: C, 74·99; H, 5·38; N, 12·4%).

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