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POTENTIAL ANTIBACTERIAL AGENTS

Part II. Synthesis of substituted N-Antipyrinyl methylenebenzohydrazides and 2-Anti-pyrinyl-5-aryl-1,3,4-oxadiazoles

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Condensation of 4-formylantipyrine with substituted benzohydrazides (Ia-e) afforded substituted antipyrinylmethylenebenzohydrazides (IIa-e). On treatment with bromine-acetic acid-sodium acetate (anhyd.), compounds IIa-d readily cyclized to the corresponding 2-antipyrinyl-5-aryl-1,3,4- oxadiazoles IIIa-d, while compound IIe under similar treatment furnished the hitherto unreported dibromo compound IIIe. Antibacterial activity of compounds synthesised was also evaluated.

Key words: Antipyrine, Benzohydrazides and 2-antipyrinyl-5-aryl- 1,3,4-oxadiazoles.

Introduction

Structure activity consideration can provide a useful guide when synthesising biologically active compounds. It is known that slight structural variation may cause significant changes in the biological activity of the drug molecule. For example pyrazole derivatives, such as 3,5-disubstituted pyrazoles and its metabolite 5-substituted pyrazole-3-carboxylic acid were shown to have potent hypoglyceamic activity [1-5]. Similarly pyrazolone derivatives, for example, antipyrine [6] and its 4-substituted derivative, 'Metamizol' [7] were reputed as analgesic, antipyretic and anti-inflammatory agents. Recently, both antipyrine and metamizol were found to cause bone marrow toxicity (agranulocytosis) and hence are vanishing from the therapeutic scene in most countries [7]. It was, therefore, felt worth while to synthesise new 4-substituted antipyrines and evaluate their biological activity.

It has been reported that certain acid hydrazides such as p-aminosalicyclohydrazide [8] and cyanoacetohydrazide [9] have antimicrobial activity. These acid hydrazides also serve as key intermediates in the preparation of oxadiazoles [10], which are biologically active compounds and find use as antihistamine [11], ulcer inhibitor [12], anticonvulsant [13], and pregnancy interceptive agents [14]. The present paper describe the synthesis of substituted N' antipyrinyl-methylenebenzohydrazides and their cyclization to the corresponding oxadiazoles. The synthesised compounds were also screened for antibacterial activity.

Materials and Methods

Melting points were taken on a Buchi 510 melting point apparatus and are uncorrected. The IR spectra were measured in KBr on a JASCO A-302 spectrophotometer. The ^{1}H-nmr spectra were recorded in $CDC1_3$ on a Brucker AM 300 ASPECT 3000 spectrometer using TMS as internal reference. High resolution mass spectra were taken on Finningen MAT 112S and MAT 312 spectrometers connected to PDP 11/34 and MAT 188 computer.

Benzohydrazides (Ia-e). The hydrazides Ia-e used in this work were prepared according to known procedure [21] by heating the methylester of the acid with hydrazine hydrate on a water bath.

Preparation of substituted N'-(antipyrinylmethylene) benzohydrazides (IIa-e). A mixture of the substituted benzohydrazides Ia-e (0.01 mole) and 4-formylantipyrine (0.01 mole) in 95% ethanol (200 ml) was refluxed on a water bath for 4 hrs. The resulting solution was concentrated in vacuo and cooled. The separated solid was filtered, washed with ethanol and crystallized from methanol to give substituted N- (antipyrinylmethylene) benzohydrazides IIa-e (Table 1).

Preparation of 2-antipyrinyl-5-aryl-1,3,4-oxadiazoles (IIIa-d). Bromine (0.05 mole) in glacial acetic acid (2.68 ml) was added dropwise with stirring to a mixture of IIa (and similarly for IIb-d) (0.012 mole), sodium acetate anhydrous (0.1 mole) and glacial acetic acid (25 ml). After the addition was completed, stirring was continued for 15 mins more and during this period the red colour of the solution faded away with the deposition of a white precipitate of sodium bromide. The mixture was poured in water (200 ml) and extracted with methylene chloride (3 x 50 ml). Removal of the solvent and crystallization of the resulting gummy residue from appropriate solvent furnished the 2-antipyrinyl-5- aryl-1,3,4-oxadiazoles IIIa-d (Table 2).

Preparation of N-(antipyrinylmethylene)-3,5-dibromo-2- hydroxybenzohydrazide (IIIe). Compound IIe on reaction similar to that described above for IIa-d, afforded a solid which on crystallization from glacial acetic acid furnished N-

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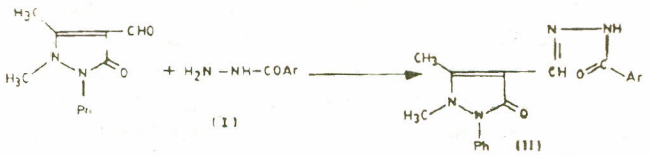
(antipyrinylmethylene)-3,5-dibromo-2-hydroxy-benzohydrazide IIIe, as cream coloured crystals, m.p. 295-6° (yield 86%) IR: 3420 (- OH), 3150 (-NH), 1650 (C=N) and 1658cm^{-1}(C=O). Mass: m/z 508 (M^+, 10%), 428 (8%), 350 (6%), 319 (5%), 270 (29%), 231 (45%), 214 (95%), 199 (68%), 173 (14%), 121 (50%) and 77 (base peak, 100%). NMR : δ 2.37 (3H,S,-C-CH_3), δ 3.24 (3H,S,-N-CH_3), δ 7.15 (IH,S,-CH=N), δ 7.3-7.6 (5H,m,Ar-H of ring A), δ 8.13 (IH,d,H_b of ring B, J=2.1 Hz), δ 7.74 (IH,d,H_d of ring B, J=2.1 Hz), δ 1.78 (2H, broad singlet, overlapping peaks of -NH and -OH).

Discussion

Condensation of 4-formylantipyrine with substituted benzohydrazides Ia-e afforded the corresponding antipyrinylmethylenebenzohydrazides IIa-e (Scheme-I). The presence of (R-CH=N-NH-CO-Ar) is evident from the IR spectra. The molecular ion peaks and fragmentation pattern



Ar

a= (C_6H_5)
b= (p-$CH_3C_6H_4$)
c= p-$CH_3OC_6H_4$)
d= (p-ClC_6H_4)
e= (0-HOC_6H_4)

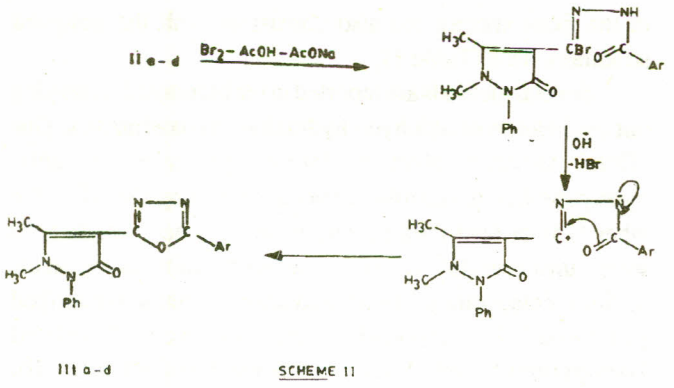
in the mass spectra are also consistant with the assigned structures IIa-e (Table 1).

Several methods are reported in the literature for carrying out cyclization of aldehyde hydrazides to oxadiazoles. Our efforts to accomplish oxidative cyclization of anti-pyrinylmethylenebenzohydrazides IIa-e using HgO/I_2 in dry ether [15] or lead tetra-acetate in methylene chloride [16] were unsuccessful. However, when bromine-acetic acid-sodium acetate (anhyd.) was used after the method described by Gibson [17], compounds IIa-d readily cyclized to afford 2-antipyrinyl-5-aryl- 1,3,4-oxadiazoles IIIa-d (Scheme II). The formation of oxadiazoles is evident from their spectral data (Table 2). The molecular ion M^+ of oxadiazoles IIIa-d, is two mass units less than the M^+ of the corresponding hydrazides IIa-d, suggesting that oxidative cyclization has occured. Also the absence of a signal for the methine proton (R-*CH*=N-) in the n.m.r. spectra and no absorption for (-NH) group in the region 3550-3150cm^{-1} in the IR. spectra of IIIa-d, supports the assignment of the oxadiazoles structures. As for mechanism, it has been reported that the formation of oxadiazoles is facilitated by the *in situ* generation of a reactive intermediate, nitrilimine (R-C^+=N-N^--CO-Ar) which cyclises intramolecularly to furnish oxadiazoles [18,19]. The sequence of reactions involved, is presented in Scheme II.

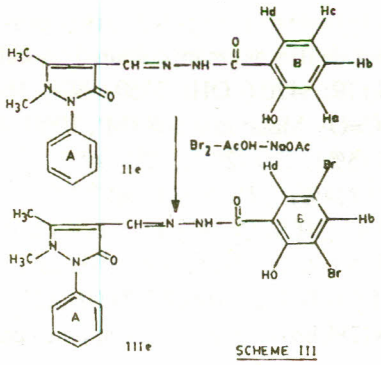
It was interesting to note that when compound IIe [20] was similarly treated with bromine-acetic acid-sodium acetate (anhyd.), it did not cyclise to oxadiazole but instead, afforded a dibromo compound which on the basis of its spectral data

TABLE 1. ANALYTICAL DATA FOR SUBSTITUTED N'-(ANTIPYRINYLMETHYLENE) BENZOHYDRAZIDES (IIa-e)

Compound	MP°C	Solvent Yield (%)	IR:(KBr)Cm^{-1}	MS: m/z (R.I.%)
IIa $C_{19}H_{18}N_4O_2$	216	MeOH 70	3550,2950,1678,1630, 1600,1570,775,700	M^+334(13),242(5),213(33) 201(18),171(3),136(12), 105(100),93(8),77 (91)
IIb $C_{20}H_{20}N_4O_2$	190	MeOH 60	3450,3280,2950,1665,1630 1610,1565,745,700,670	M^+348(4),319(1),291(1), 256(2),213(26),200(14), 171(4),119(100),105(10),91(82)
IIc $C_{20}H_{20}N_4O_3$	225	MeOH 83	3400,3160,3040,2940,1664 1636,1605,1565,845,758	M^+ 364(37),307(2),272(5), 213(74),201(31),151(1), 135(100),121(98.8),107(6.6)
IId $C_{19}H_{17}N_4O_2Cl$	222	MeOH 74	3400,3040,1675,1595,1540 1480,1450,750,700	M+368(68),276(8.5),209(100), 201(8.5),139(51),121(24), 111(30),105(10),93(11),56(95)
IIe $C_{19}H_{18}N_4O_3$	218 (lit(20)-214-6)	MeOH 86	3450,3070,2785,1642,1590, 1500,752,690,652	M+350(40),319(1),283(1),258(1), 230(46),214(76),200(19),180(7), 152(13),121(94),105(14),93(46),55(100)



SCHEME II



SCHEME III

TABLE 2. ANALYTICAL DATA FOR 2-ANTIPYRINYL-5-ARYL-1, 3, 4-OXADIAZOLES (IIIa-d)

Compound	MP°C	Solvent Yield(%)	NMR ($CDCl_3$) C-CH_3	N-CH_3	OCH_3	Atomatic Protons	IR: (KBr)Cm^{-1}	MS: m/z (R.I.%)
IIIa $C_{19}H_{16}N_4O_2$	178	EtOH 88	2.6,S	3.2,S	–	*7.39(5)m **7.29(3)t *7.04(2)m	3452,3080,1690,1592, 1552,1530,1205,1070, 780,755,695	M^+332(54),317(2),275(2), 240(17),215(32),199(8), 77(30),56(100)
IIIb $C_{20}H_{18}N_4O_2$	138	MeOH/ Ether 66	2.3,S 2.7,S	3.2,S	–	*7.35(5)m **7.2(2)m **7.9(2)m	3440,3200,1660,1602, 1585,1565,1505,1080, 830,760.	M^+346(100),331(3),317(2), 289(5),254(22),215(76), 156(16),119(68),105(22), 91(87),77(65),65(33).
IIIc $C_{20}H_{18}N_4O_3$	192	EtOAc 50	2.68,S	3.25,S	3.8,S	*7.33(5)m **6.87(2)d J_o=9.6Hz **7.98(2)d J_o=9.6Hz	3400,2820,1665,1635 1595,845,745.	M^+362(100),347(2),333(1.9), 305(3.6),277(5.3),270(5.3), 215(29.7),135(24).
IIId $C_{19}H_{15}N_4O_2Cl$	205	EtOAc 25	2.7,S	3.3,S	–	*7.3(5)m **7.3(2)m **8 (2)d J_o=8.4Hz	3360,1660,1600,1550, 1250,1175,1020,820 800,700.	M^+366(100),274(33),233(15), 215(62),139(22),82(77)

*Aromatic protons of antipyrine moiety. **Aromatic protons of 5-aryl group.

was formulated as N'-(antipyrinylmethylene)-3,5-dibromo-2- hydroxybenzohydrazide IIIe, (Scheme III). In the mass spectrum, the molecular ion M^+ appeared at 508 corresponding to the molecular formula $C_{19}H_{16}N_4O_3Br_2$. The absorption at 3150cm^{-1} for (-NH) group in the IR. spectrum and particularly the singlet at δ 7.15 for the methine proton (-CH=N-) in the n.m.r. spectrum of IIIe ruled out cyclization or even formation of bromohydrazide. To locate the position of the two bromine atoms, the n.m.r. spectra of IIe and IIIe (Table 3) were compared. It was observed that both spectra were similar except for ring B. In the n.m.r. spectrum of IIIe, the two doublets appearing at δ 8.13 (IH,d,H_b J=2.1Hz) and δ 7.74 (IH,d,H_d J=2.1Hz) were assigned to the two protons of ring B. The low coupling constant J=2. 1Hz indicated that these protons were meta-oriented. This substitution pattern allowed the placement of bromine atoms at position 3 and 5 of ring B in IIIe. The preferential bromination of ring B, seems to have been facilitated by the presence of -OH group in it.

Compounds IIa-e and IIIa-e were also tested for anti-bacterial activity against *Bacillus subtilis, Pseudomonas*

TABLE 3. 1H-NMR DATA FOR N'-(ANTIPYRINYLMETHYLENE)-2-HYDROXYBENZOHYDRAZIDE (IIe) AND N' (ANTIPY)-3,5-DIBROMO-2- HYDROXYBENZOHYDRAZIDE (IIIe)

Protons	Compound IIe δ	Compound IIIe δ
-C-CH_3	2.39 (3H,S)	2.37 (3H,S)
-N-CH_3	3.31 (3H,S)	3.24 (3H,S)
-N-CH	7.17 (1H,S)	7.15 (1H,S)
Aromatic Protons of Ring A.	7.3-7.5 (5H, m)	7.3-7.6 (5H,M)
Aromatic Protons of Ring B.		
H_a	7.93 (1H,dd,Jo=8.1Hz Jm=1.5Hz)	Br
H_b	6.79 (1H,t,J_o=8.1Hz Jm=1.02Hz),	8.13 (1H,d Hz) Jm=2.1
H_c	7.28 (1H,t,J_o=8.1Hz Jm=1.5Hz)	Br
H_d	6.(1H,dd,J_o=9.3Hz Jm=0.9Hz	7.74 (1H,d, Jm=2.1Hz)
NH and -OH	1.57 (2H, broad singlet) Overlapping peaks of -NH and -OH	1.77 (2H,broad singlet) Overlapping peakof -NH and -OH

sp., *Streptococcus faecalis* and *Staphylococcus aureus* (Gram positive), *Escherichia coli and Salmonella typhi* (Gram negative) using concentration levels 1.25 - 5.0 mg/ml. These compounds, however did not show any significant activity

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