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Note

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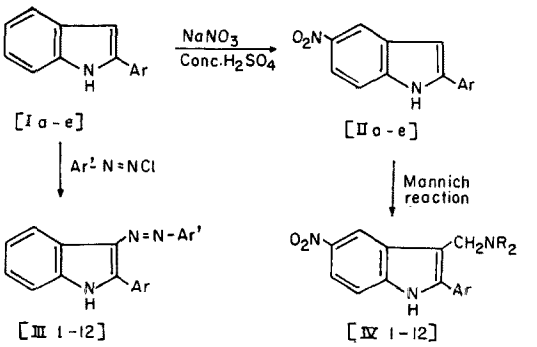
Various biological activities[1~3] like antidepressive,[4] anorectic,[5] hallucinogenic,[6] antiinflammatory,[7] tuberculostatic,[8] antibacterial *etc.* have been attributed to indole derivatives.[9~11] Baker *et al.*[12] have reported that the introduction of nitro and trifluoromethyl groups in the phenyl ring of acetanilides enhances the antibacterial activity against *S. aureus*. Keeping these observations in view, 3-aryldiazo-2-fluorophenylindoles and 3-dialkylaminomethyl-2-fluorophenyl-5-nitroindoles have now been synthesized; the former by the action of appropriate aryldiazonium chloride on 2-fluorophenylindoles[13] and the latter by the Mannich reaction of 2-fluorophenyl-5-nitroindoles[14] (Scheme 1).



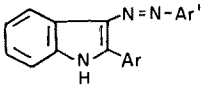
III 1~12 Ar and Ar′=Substituted fluorophenyl.
IV 1~4 Ar=4-FC_6H_4; NR_2=**1**, Dimethylamino, **2**, morpholino; **3**, piperidino- and **4**, diethylamino-.
IV 5~7 Ar=4-F, 3-MeC_6H_3; NR_2=**5**, Dimethylamino; **6**, piperidino-, **7**, diethylamino-.
IV 9 Ar=4-F,3-MeC_6H_3; NR_2=Dimethylamino-.
IV 8, 10~12 Ar=3-Cl,4-FC_6H_3; NR_2= **8**, Dimethylamino-, **10**, diethylamino-, **11**, morpholino-, **12**, piperidino-.

SCHEME 1

EXPERIMENTAL

2-(4′-Fluorophenyl)indole, 2-(4′-fluoro-3′-methylphenyl)indole, 2-(4′-fluoro-2′-methylphenyl)indole, 2-(2′-fluoro-5′-methylphenyl)indole and 2-(3′-chloro-4′-fluorophenyl)indole were prepared by Fischer Indole Synthesis.[15] These indoles were nitrated with sodium nitrate in sulphuric acid (conc.) to give corresponding 5-nitro derivatives (II-a-e).[16] 3-Aryldiazo-2-fluorophenylindoles (III 1~12) were prepared by the coupling of aryldiazonium chlorides (0.01 mole) with indoles

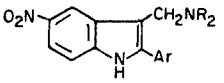
TABLE I. ANALYTICAL DATA OF 3-ARYLDIAZO-2-(FLUOROPHENYL)INDOLES



S.No.	Substituent in Ar′	Substituent in Ar	Molecular formula	Yield %	mp °C	N% Calcd.	N% Found
III 1	4-F	4-F	$C_{20}H_{13}F_2N_3$	74	236	12.61	12.52
III 2	4-F	–	$C_{20}H_{14}FN_3$	72	240	13.33	13.96
III 3	4-F	4-F,3-CH_3	$C_{21}H_{15}F_2N_3$	64	158	12.10	12.04
III 4	4-F	4-F,2-CH_3	$C_{21}H_{15}F_2N_3$	63	80~83	12.10	11.92
III 5	3-CF_3	4-F	$C_{21}H_{13}F_4N_3$	59	165	10.96	11.34
III 6	4-Br	4-F	$C_{20}H_{13}FBrN_3$	67	175	10.66	10.65
III 7	3-CF_3	2-F,5-CH_3	$C_{22}H_{15}F_4N_3$	56	147	10.57	10.64
III 8	4-F	2-F,5-CH_3	$C_{21}H_{15}F_2N_3$	58	108	12.10	11.96
III 9	3-CF_3	4-F,3-Cl	$C_{21}H_{12}F_4ClN_3$	64	126	10.07	10.14
III 10	3-NO_2	4-F	$C_{20}H_{13}FN_4O_2$	63	221	15.55	15.33
III 11	4-Br	4-F,3-Cl	$C_{20}H_{12}FClBrN_3$	61	126	9.80	9.72
III 12	4-NO_2	4-F,3-Cl	$C_{20}H_{12}FClN_4O_2$	52	240	14.20	14.32

† Studies in Potential Organo-Fluorine Antibacterial Agents. Part IV.

TABLE I. (Contd.) 2-SUBSTITUTEDARYL-3-(DIALKYLAMINOMETHYL)-5-NITROINDOLES



S.No.	Substituents in Ar	$-NR_2$	Molecular formula	Yield %	mp °C	N%	
						Calcd.	Found
IV 1	4-F	Dimethylamino-	$C_{17}H_{17}FN_3O_2$	38	184	13.33	13.09
IV 2	4-F	Morpholino-	$C_{19}H_{19}FN_3O_3$	46	200	11.80	11.62
IV 3	4-F	Piperidino-	$C_{20}H_{21}FN_3O_2$	38	174	11.90	11.80
IV 4	4-F	Diethylamino-	$C_{19}H_{21}FN_3O_2$	30	128	12.28	12.04
IV 5	4-F,2-Me	Dimethylamino-	$C_{18}H_{19}FN_3O_2$	40	183	12.80	12.56
IV 6	4-F,2-Me	Piperidino-	$C_{21}H_{23}FN_3O_2$	32	127	11.40	11.19
IV 7	4-F,2-Me	Diethylamino	$C_{20}H_{23}FN_3O_2$	28	119	11.80	11.48
IV 8	3-Cl,4-F	Dimethylamino-	$C_{17}H_{16}ClFN_3O_2$	42	166	12.10	12.00
IV 9	4-F,3-Me	Dimethylamino-	$C_{18}H_{19}FN_3O_2$	48	155	12.80	12.59
IV 10	3-Cl,4-F	Diethylamino-	$C_{19}H_{20}ClFN_3O_2$	35	140	11.15	11.12
IV 11	3-Cl,4-F	Morpholino-	$C_{19}H_{18}ClFN_3O_3$	45	224	10.79	10.58
IV 12	3-Cl,4-F	Piperidino-	$C_{20}H_{20}ClFN_3O_2$	40	185	10.85	10.80

TABLE II. ANTIBACTERIAL ACTIVITY OF COMPOUNDS AGAINST *S. aureus*

Compd. Nos.	Mean value of area of inhibition in mm (5 μg/disk)	Mean value of area of inhibition in mm (7 μg/disk)	Mean value of area of inhibition in mm (10 μg/disk)	Observed results with the test species	MIC value (μg/disk)
III 1	8.0	10.7	14.0	Sensitive	2
III 2	8.0	8.7	13.0	Sensitive	2
III 3	10.0	10.7	11.0	Moderately sensitive	3
III 4	9.0	10.7	11.0	-do-	3
III 5	8.7	10.7	14.2	Sensitive	2
III 6	8.7	8.7	8.7	Moderately sensitive	4
III 7	8.5	10.0	10.0	-do-	4
III 8	8.0	10.0	11.0	-do-	3
III 9	8.0	8.7	8.7	-do-	4
III 10	8.0	9.7	10.0	-do-	3
III 11	7.0	7.7	8.3	-do-	4
III 12	7.0	7.5	10.0	-do-	4
IV 1	7.7	10.0	10.0	Moderately sensitive	4
IV 2	8.0	8.0	8.0	-do-	4
IV 3	7.3	7.3	8.0	-do-	4
IV 4	8.0	10.0	10.0	-do-	4
IV 5	8.7	12.0	13.0	Sensitive	3
IV 6	11.3	12.0	12.3	-do-	2
IV 7	8.0	10.0	10.0	Moderately sensitive	4
IV 8	9.7	9.7	10.0	-do-	3
IV 9	8.3	9.3	10.0	-do-	3
IV 10	10.7	10.7	10.7	-do-	2
IV 11	10.8	10.7	12.3	Sensitive	2
IV 12	10.7	10.7	11.0	Moderately sensitive	3

Sensitive = Zone of inhibition between 11.1 ~ 14.0 mm
Moderately sensitive = Zone of inhibition between 8.0 ~ 11.0 mm.

(0.01 mole) in ethanol/glacial acetic acid (100 ml) at 0~5°C in the presence of sodium acetate.[13] The characteristic and analytical data are given in Table I. 3-Dialkylaminomethyl-2-fluorophenyl-5-nitroindoles (IV 1~12) were synthesized by the Mannich reaction of corresponding 5-nitroindoles (II a~e).[14]

The antibacterial activity against *E. coli* and *S. aureus* was tested by disk diffusion method.[17] The area of the inhibition of growth of bacteria produced by the diffusion of the compound from the disk into the surrounding medium was measured. Three replicates of each test compound, with varying concentrations, were used. Minimum Inhibitory Concentration was measured for each compound by taking different concentrations.

RESULTS AND DISCUSSION

The IR spectra showed absorption between 3350~3400 cm^{-1} due to >NH stretching vibrations. 3-Aryldiazoindoles exhibited absorption bands between 1580~1610cm^{-1} (N=N) and 1060~1180cm^{-1} (C–N). In PMR spectra, NH resonance signal occurred between δ 7.8~8.2 ppm and phenyl protons were observed at δ 6.8~7.4 ppm in all indole derivatives.

All these compounds were unable to inhibit the growth of *E. coli* but inhibited the growth of *S. aureus*. Compound Nos. III1, III2, and III5 showed pronounced activity. In these compounds fluorine and trifluoromethyl groups are present in the phenyl ring. We have not observed any significant change in the activity due to nitro group. Compound Nos. IV5, IV6 and IV11 also showed pronounced activity against *S. aureus*. The MIC of these compounds was between 2.0~4.0 μg per disk, while many mitomycin derivatives (indole derivatives) have been reported to possess MIC between 1.56 to 12.5 μg per ml.[18,19]

The results have been summarised in Table II.

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