Pak. j. sci. ind. res., vol. 33, no. 4, April 1990

SYNTHESIS OF SOME 9-ETHOXYPSORALENE DERIVATIVES OF POTENTIAL BIOLOGICAL ACTIVITY

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(Received March 25, 1989; revised April 21, 1990)

Several chemical reactions of 9-ethoxypsoralene are described, including nitration, reduction, bromonation and thionation reactions. The amine derivative was acetylated to mono and di-acetyl derivatives, also it was reacted with allylbromide. Some of the new derivatives were tested against some micro-organisms.

Key words: 9-Ethoxypsoralene, 9-Ethoxy furo-thiocoumarin.

Introduction

The world wide interest of psoralene derivatives for their biological activities such as vasodilatory, anticoagulant, estrogenic, diuretic, antibacterial, respiratory stimulant and photosensitizing agents [1-5] promoted us to study some reactions on 9-ethoxypsoralene (II), for continuation of our previous work [6], starting with 9-hydroxypsoralene (I) [7].

Experimental

All melting points are uncorrected. The ^{1}H NMR spectra were run in $CDCl_3$/DMSO on an EM 360/390 nmr spectrometer. MS were done using a MAT 112 spectrometer. 9-Hydroxypsoralene (I) and 9-ethoxypsoralene (II) were prepared according to Schonberg [7]. The mass spectrum of compound (II) m/z; rel. int.); is as follows: M^+ 230 (47%), 201 (M^+-C_2H_5, CO; 62%), 145 (M^+-C_2H_5, 2C0; 10%), 117 (5%) and 89 (23%).

5-Nitro-9-ethoxypsoralene (III). 9-Ethoxypsoralene (II) was treated with concentrated HNO_3 according to Brokke [8] to obtain the product (III) in 90% yield. The mass spectrum of this compound (m/z; rel. int.): M^+275 (31%), 246 (M^+-C_2H_5; 56%), 216 (M^+-C_2H_5, NO; 20%), 201 (M^+-C_2H_5, NO_2; 100%), 188 (M^+-C_2H_5, NO, CO; 9%)$_2$ 160 (M^+-C_2H_5, 2CO; 4%), 132 (2.5%), 104 (2.5%), 173 (M^+-C_2H_5, NO_2 2CO; 12%), 117 (16%) and 89 (13%).

5-Amino-9-ethoxypsoralene (IV). 5-Nitro-9-ethoxypsoralene (III) was reduced with $SnCl_2$ and tin granules in the same manner as 5-nitro-4-methoxypsoralene [8] to obtain the product (IV) in 55% yield. The IR spectrum of IV showed bands at 1710 cm^{-1} (C=0), 3360 cm^{-1} (NH_2).

5-Monoacetylamino-9-ethoxypsoralene(V). 5-Amino-9-ethoxypsoralene (IV) (0.001mol) was dissolved in a mixture of acetic anhydride and acetic acid (4:3; 40 ml), and heated on a water bath for one hour, then cooled and diluted with C_2H_5OH/H_2O (1:1). The deposited crystals were filtered off and crystallised from ethanol to give the product (V) in 80% yield. The IR spectrum of (V) showed a characteristic band at 3310 cm^{-1} (NH).

5-Bromo-9-ethoxypsoralene (VI). 9-Ethoxypsoralene (II) (0.0022 mol) in $CHCl_3$ (10 ml) was allowed to stand for 5 min. with bromine (0.0022 mol), then concentrated to a small volume and the solid obtained was filtered off and crystallised from ethanol to give (VI) in 70% yield. The MS spectrum of (VI) (m/z; rel. int.); M^+ 308 and 310 (d, Br; 20%), 279 and 281 (M^+-C_2H_5; 46%), 251 and 253 (M^+-C_2H_5, CO; 7%), 223 and 226 (M^+-C_2H_5, 2CO; 5%), 201 (M^+-C_2H_5, Br, 100%), 173 (M^+-C_2H_5, Br, CO; 10%), 145 (16%), 117 (10%), 89 (10%) and 63 (8%). The ^{1}H NMR spectrum of compound (VI) showed signals at δ =6.58 and 8.2 ppm (2H, d, C-3 and C-4 protons, $J_{3,4}$= 10 Hz),δ =6.92 ppm and 7.8 ppm (2H, d, C-6 and C-7 protons, $J_{6,7}$ = 3Hz), δ = 1.55 ppm (3H, t, side chain protons) and δ = 4.66 ppm (2H, q, CH_2 side chain).

5,6,7-Tribromo-9-ethoxypsoralene (VII). A solution of 9-ethoxypsoralene (II) (0.0022 mol) in $CHCl_3$ (50 ml) was allowed to stand for 5 min. with bromine (0.006 mol) and after the usual work-up the product was obtained as pale yellow needles in 60% yield. Thus MS spectrum of compound (VII) (m/z; rel. int.): M^+- 446, 470 and 472 as quartet lines (1:3:3:1), 386, 388 and 390 (1:2:1), M^+ -Br, 4%) 308 and 310 (1:1), M^+-2 Br, 46%), 280 and 282 (1:1), M^+ - Br, C_2H_5, 2CO; 5%), 201 (100%), 173 (10%) and 145 (15%).

6,7-Dihydro-9-ethoxypsoralene (VIII). The hydrogenation of compound (II) was carried out at atmospheric pressure for 2 hrs. using 10% Pd/C and worked up in the usual manner. The dihydro-product was crystallised from ethanol/water in 70% yield.

3-Nitro-6, 7-dihydro-9-ethoxypsoralene (IX). 6,7-Dihydro-9-ethoxypsoralene (VIII) (0.0022 mol) was stirred with 15 ml of a (1:2) solution of concentrated HNO_3 in glacial acetic acid at 20°for 15min., then poured into cold water. The product was crystallised from dioxane to give (IX) in 70% yield.

3,5-Dibromo-6, 7-dihydro-9-ethoxypsoralene (X). A solution of (VIII) (0.0022 was stirred at room temp. for 5 min. with bromine (0.004 mol) in chloroform (30 ml), and after usual work-up gave 50% yield of product X, and crystallised from ethanol.

9-Ethoxyfuro-(3,2-g)-thiocoumarin (XI). 9-Ethoxypsoralene (II) (0.0076 mol) was refluxed for 2 hrs. within 3.5

grams of phosphorous pentasulphide in 75 ml xylene. The mixture was filtered and cooled. The product was collected and crystallised from ether to give (XI) in 55% yield.

5-Diacetylamino-9-ethoxypsoralene (XII): A mixture of (0.002 mol) monoacetyl (V) in excess acetic anhydride was refluxed for 6 hr, cooled and diluted with 80% ethanol. The deposited crystals were filtered off and crystallised from ethanol to give (XII) in 50% yield.

5-Bromo-9-ethoxyfuro-(3, 2-g)-thiocoumarin (XIII). 9-Ethoxyfuro-(3, 2-g)-thiocoumarin (XI), (0.001 mol) in $CHCl_3$ (5 ml) was stirred at room temperature for one hr with bromine (0.001 mol), then cooled and the deposited material was filtered off, washed with cold ethanol and crystallised from ether to give (XIII) in 55% yield.

5-Monoallylamino-9-ethoxypsoralene. (XIV). 5-Amino-9-ethoxypsoralene *(IV)* (0.001 mol) was refluxed with (0.001 mol) allyl bromide in dry acetone (10 ml) and anhydrous potassium carbonate for 10 hr. The reaction mixture was worked-up as usual, and the product XIV crystallised from ethanol (yield 40%).

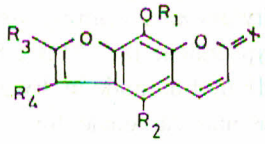
5-(2-Aminopyridino)-9-ethoxypsoralene. A mixture of 5-bromo-9-ethoxypsoralene (V) (0.001 mol), 2-aminopyridine (0.001 mol) in 10 ml dry acetone and anhydrous potassium carbonate was refluxed for 8 hr. The solvent was evaporated and the reaction mixture poured into crushed ice, the deposited material was filtered off and crystallised from ethanol to give (XV) in 48% yield.

Melting points, analytical and biological test data of compounds (II-XV) are given in Table 1.

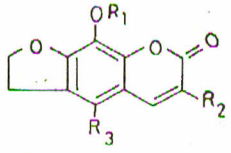
Table 1

Compd. No.	m.p. °C	Formula (molecular mass)		Analysis Cald./Found C%	H%	N%	Biological activity of some micro-organisms. [9] a	b	c	d	e	f	g	h
I	225 (Lit.)						+	+	–	+	–	–	–	–
II	115-6	$C_{13}H_{10}O_4$	(230.21)	67.82 67.85	4.37 4.80		+	+	+	+	–	–	–	–
III	212-4	$C_{13}H_9NO_6$	(275.20)	56.73 56.86	3.29 3.06	5.09 5.43	+	++	–	+	–	–	–	–
IV	180-2	$C_{13}H_{11}NO_4$	(245.21)	63.63 63.85	4.51 4.63	5.70 5.83	+	+	–	+	–	–	–	–
V	270-2	$C_{15}H_{13}NO_5$	(287.25)	62.73 62.67	4.52 4.08	4.87 4.96	–	+	–	+	–	–	–	
VI	156-8	$C_{13}H_9BrO_4$	(309.20)	50.51 50.22	2.90 2.78		–	+	–	+	+	–	–	–
VII	118-20	$C_{13}H_9Br_3O_4$	(469.20)	33.29 32.98	1.93 2.08		++	++	–	+	+	–	–	–
VIII	110-12	$C_{13}H_{12}O_4$	(232.22)	67.23 67.25	5.20 5.20		–	–	–	–	+	–	–	–
IX	182-4	$C_{13}H_{11}NO_6$	(277.21)	56.32 55.92	3.99 4.09	5.05 5.32	–	++	–	+	+	+	–	–
X	248-50	$C_{13}H_{10}Br_2O_4$	(390.21)	40.03 39.89	2.58 3.05		++	++	–	+	+	–	–	–
XI	132-4	$C_{13}H_{10}O_3S$	(246.27)	63.39 63.71	4.09 4.35		+	++	-	+	+	-	–	–
XII	188-90°	$C_{17}H_{15}NO_6$	(329.17)	62.02 62.21	4.56 4.23	4.25 – –	-	+	-	+	-	-	-	-
XIII	181-83	$C_{13}H_9Br\ O_3S$	(325.09)	48.02 48.15	2.77 2.65	– – – –	++	++	-	+	+	-	-	-
XVI	133-35	$C_{16}H_{15}NO_4$	(285.16)	67.39 67.51	5.26 5.34	4.90 4.78	+	+	+	+	-	+	+	-
XV	141-43	$C_{18}H_{14}N_2O_4$	(322.18)	67.09 67.26	4.35 4.25	8.69 8.83	-	+	-	-	+	-	-	-

(a) *S . aureus.*, (b) *B. subtilis.*, (c) *P. aeruginose.*, (d) *E. coli.*, (e) *C. freundii.*, (f) *P. mirabilis.*, (g) *K. pneumonia* , (h) *S. cerevisieue.*,



Compd. No.	R_1	R_2	R_3	R_4	X
I	H	H	H	H	O
II	C_2H_5	H	H	H	O
III	C_2H_5	NO_2	H	H	O
IV	C_2H_5	NH_2	H	H	O
V	C_2H_5	$NHCOCH_3$	H	H	O
VI	C_2H_5	Br	H	H	O
VII	C_2H_5	Br	Br	Br	O
XI	C_2H_5	H	H	H	S
XII	C_2H_5	$N(COCH_3)_2$	H	H	O
XIII	C_2H_5	Br	H	H	S
XIV	C_2H_5	$HNCH_2CH=CH_2$	H	H	O
XV	C_2H_5	HN 	H	H	O



VIII , $R_1 = C_2H_5$, $R_2 = H$, $R_3 = H$
IX , $R_1 = C_2H_5$, $R_2 = NO_2$, $R_3 = H$
X , $R_1 = C_2H_5$, $R_2 = R_3 = Br$

Chart I

Results and Discussion

Nitration of (II) afforded 5-nitro-9-ethoxyposoralene (III). Compound (IV) was allowed to react with acetic anhydride, allylbromide and 2-aminopyridine to obtain the derivatives (V, XII, XIV) and (XV) respectively.

Compound II was allowed to react with one mole bromine to produced monobromo derivative VI while in case of excess of bromine, triboromo compound VII was afforded.

The thionation of compound II using phosphorous pentasulphide afforded compound XI, which when reacted with one mole bromine, the monobromo-derivative XIII was obtained.

The biological effect of 9-ethoxypsoralene derivatives was examined on some micro-organisms such as *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, Proteus mirabilis, Klebsiella pneumonia, Bacillus subtilis and Saccharomyces cerevisia.* The obtained results indicated that compounds III, VII, IX, X, XI and XIII possess moderate antibacterial activity, whereas, compounds I, II, IV, V, VI, XII, XIV and XV possess slight antibacterial activity as listed in Table 1. The test was carried out according to [9].

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