Potential Anticonvulsants. V. The Condensation of Isatins with *C*-Acetyl Heterocyclic Compounds

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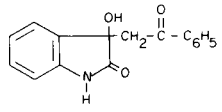
Received November 9, 1981

A number of *C*-acetyl heterocyclic compounds were condensed with isatin and substituted isatins to give a series of 3-hydroxy-3-substituted oxindoles. The products from 2-acetylfuran and isatin, 2-acetylthiophene and isatin, and 2-acetylpyridine and 1-methylisatin were active at 100 mg/Kg in the maximal electroshock seizure test.

J. Heterocyclic Chem., **19**, 589 (1982).

Earlier we reported (1,2) that the oxindole **1** exhibited anticonvulsant activity in the maximal electroshock seizure test (MES) (3) with an ED_{50} of 102 mg/Kg and a protective index (PI) of about 4. It was also reported that **1** was inactive in the pentylenetetrazol seizure threshold test (Met) (3). Substitutions in the *p*-position of the phenyl group in **1** as well as replacement of the phenyl group by 3-pyridyl, 3-indolyl, and ferrocenyl caused loss of activity in the MES test (1). The compound **2** formed from the reaction of isatin and 2-acetylpyridine; however, was active at 300 mg/Kg in the MES test.

In view of the fact that some activity was found in **2** it was deceided to investigate the synthesis and anticonvulsant activity of a series of 3-hydroxy-3-substituted-oxindoles derived from 2-acetylpyridine and substituted isatins. At the same time a variety of other *C*-acetyl heterocyclic compounds were also condensed with isatins in the presence of diethylamine to give the oxindoles of type **3** shown in Table I. All of the compounds exhibited spectra consistent with the structure.



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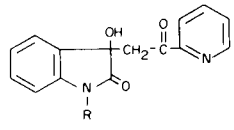
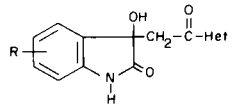


2 R = H
4 R = CH_3



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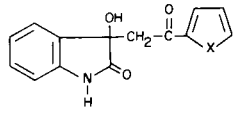


5 X = O
6 X = S

With the exception of **4**, which had an activity of 100 mg/Kg in the MES test, all of the compounds derived from 2-acetylpyridine and substituted isatins had the same activity as **2** or were inactive. Compound **4**, derived from 1-methylisatin and 2-acetylpyridine was the most active compound in this series. The products **5** and **6**, derived from reaction of 2-acetylfuran and 2-acetylthiophene, respectively, with isatin were also active at 100 mg/Kg in the MES test. All of the other products were less active or inactive.

It had been reported earlier (1,2) that dehydration of **1** and other related compounds caused loss of anticonvulsant activity. This was also true with dehydration of **5** and **6**, and the products shown in Table II were all inactive at 600 mg/Kg in both the MES and Met tests.

EXPERIMENTAL

Condensation of Isatins with *C*-Acetyl Heterocyclic Compounds.

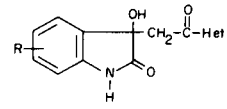
The isatin (0.01 mole) and the *C*-acetyl heterocyclic compound (0.01 mole) in 30-50 ml of absolute ethanol containing 3-4 drops of diethylamine were heated at reflux on the steam bath for about 30 minutes. After standing for several days at room temperature, the products (Table I) were collected, in good yield, by filtration.

Dehydration of 3-Hydroxy-3-substituted Oxindoles.

A mixture of 0.01 mole of **3**, 0.5 ml of concentrated hydrochloric acid, and 17 ml of glacial acetic acid were heated on the steam bath for 15-30 minutes. Addition of ethanol and standing at room temperature gave the products shown in Table II.

Table I

Condensation of Isatin with Heterocyclic Methyl Ketones



HetCOCH$_3$	R	Mp °C (a)	Formula	Analysis Calcd. / Found C	H	N	Anticonvulsant Activity (mg/Kg) (b) MES	Met
2-Acetylpyridine	H	144-146 (c)	$C_{15}H_{12}N_2O_3$	-	-	-	300	NA (d)
2-Acetylpyridine	1-CH_3	147-148	$C_{16}H_{14}N_2O_3$	68.07	5.00	9.92	100 (n)	600
				68.18	4.98	10.05		
2-Acetylpyridine	5-Br	188-189	$C_{15}H_{11}BrN_2O_3$	51.89	3.19	8.07	300	NA (e)
				51.82	3.25	8.13		
2-Acetylpyridine	5-NO_2	198-202	$C_{15}H_{11}N_3O_5$	57.51	3.54	13.41	NA (e)	NA (e)
				57.42	3.52	13.24		
2-Acetylpyridine	5-CH_3	188-189	$C_{16}H_{14}N_2O_3$	68.07	5.00	9.92	NA (e)	NA (e)
				68.05	5.06	9.88		
2-Acetylpyridine	7-Cl	177-178	$C_{15}H_{11}ClN_2O_3$	59.51	3.66	9.26	300	NA (e)
				59.67	3.66	9.28		
2-Acetylpyridine	4-Cl-7-CH_3	192-193	$C_{16}H_{13}ClN_2O_3$	60.67	4.14	8.84	NA (e)	300
				60.78	4.10	8.88		
2-Acetylpyridine	4-Cl-7-OCH_3	192-193	$C_{16}H_{13}ClN_2O_4$	57.75	3.94	8.42	NA (e)	NA (e)
				57.78	4.01	8.33		
4-Acetylpyridine	H	164-166	$C_{15}H_{12}N_2O_3$	67.15	4.51	10.44	300 (o)	NA (e,o)
				67.34	4.51	10.48		
4-Acetylpyridine	1-CH_3	128-129	$C_{16}H_{14}N_2O_3$	68.09	5.00	9.92	300 (ℓ)	300 (ℓ)
				67.95	5.01	9.94		
4-Acetylpyridine	5-Br	212-213	$C_{15}H_{11}BrN_2O_3$	51.89	3.19	8.07	NA (e)	NA (e)
				52.00	3.01	7.93		
4-Acetylpyridine	4-Cl-7-CH_3	165-166	$C_{16}H_{13}ClN_2O_3$	60.67	4.14	-	600	NA (e)
				60.31	4.54	-		
2-Acetylfuran	H	189-190 (f)	$C_{14}H_{11}NO_4$	65.36	4.31	5.44	100 (g)	NA (e)
				65.35	4.29	5.38		
2-Acetylfuran	1-CH_3	147-148	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	100	NA (e)
				66.45	4.94	5.13		
2-Acetylfuran	5-Br	209-210	$C_{14}H_{10}BrNO_4$	50.02	3.00	-	NA (e)	NA (e)
				50.07	2.94	-		
2-Acetylfuran	5-NO_2	209-210	$C_{14}H_{10}N_2O_6$	55.63	3.34	-	NA (e)	NA (e)
				55.44	3.34	-		
2-Acetylfuran	7-Cl	203-204	$C_{14}H_{10}ClNO_4$	57.64	3.46	-	NA (e)	NA (e)
				57.40	3.65	-		
2-Acetylfuran	4-Cl-7-OCH_3	201-202	$C_{15}H_{12}ClNO_5$	56.00	3.76	-	NA (e)	NA (e)
				56.02	3.81	-		
Benzofuran-2-yl methyl ketone	H	202-204	$C_{18}H_{13}NO_4$	70.35	4.26	-	NA (e)	NA (e)
				70.16	4.41	-		
2-Acetylthiophene	H	177-178	$C_{14}H_{12}NO_3S$	61.52	4.06	5.12	100 (h)	NA (e)
				61.47	4.05	5.07		
2-Acetylthiophene	1-CH_3	138-139	$C_{15}H_{13}NSO_3$	62.70	4.56	-	300	NA (e)
				62.77	4.52	-		
2-Acetylthiophene	1-$C_6H_5CH_2$	144-145 (ij)	$C_{21}H_{17}NO_3S$	69.39	4.71	-	NA (e)	NA (e)
				69.25	4.66	-		
2-Acetylthiophene	5-Br	216-218	$C_{14}H_{10}BrNO_3S$	47.74	2.86	-	NA (e)	NA (e)
				47.72	2.82	-		
2-Acetylthiophene	5-NO_2	225-227	$C_{14}H_{10}N_2O_5S$	52.82	3.17	-	NA (e)	NA (e)
				52.81	3.13	-		

Table I

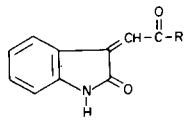
Condensation of Isatin with Heterocyclic Methyl Ketones continued

HetCOCH$_3$	R	Mp °C (a)	Formula	Analysis Calcd. / Found C	H	N	Anticonvulsant Activity (mg/Kg) (b) MES	Met
2-Acetylthiophene	7-Cl	180-181	$C_{14}H_{10}ClNO_3S$	54.64 54.64	3.28 3.27	- -	600	NA (e)
2-Acetylthiophene	4-Cl-7-OCH$_3$	208-210	$C_{15}H_{12}ClNO_4S$	53.33 52.99	3.58 3.84	- -	NA (e)	NA (e)
2-Acetyl-5-bromo-thiophene	H	170-172	$C_{14}H_{10}BrNSO_3$	47.74 47.80	2.86 3.07	- -	NA (e)	600
2-Acetyl-5-chloro-thiophene	H	156-157	$C_{14}H_{10}ClNSO_3$	54.64 54.67	3.28 3.38	- -	600	NA (e)
2-Acetyl-3-methyl-thiophene	H	200-201	$C_{15}H_{13}NSO_3$	62.70 62.84	4.56 4.50	4.88 4.84	600	NA (e)
2-Acetyl-5-methyl-thiophene	H	178-179	$C_{15}H_{13}NO_3S$	62.70 62.64	4.56 4.60	4.88 4.85	300	NA (e)
3-Acetylthiophene	H	187-188	$C_{14}H_{11}NO_3S$	61.52 61.51	4.06 4.12	5.12 5.07	600	300
3-Acetylthiophene	1-CH$_3$	161-162	$C_{15}H_{13}NSO_3$	62.70 62.82	4.56 4.58	- -	NA (e)	NA (e)
3-Acetylthiophene	5-Br	210-212	$C_{14}H_{10}BrNO_3S$	47.74 47.65	2.86 2.83	- -	NA (e)	NA (e)
3-Acetylthiophene	5-NO$_2$	231-233	$C_{14}H_{10}N_2O_5S$	52.82 52.56	3.17 3.09	- -	NA (e)	NA (e)
3-Acetylthiophene	4-Cl-7-OCH$_3$	206-208	$C_{15}H_{12}ClNSO_4$	53.33 53.32	3.58 3.82	- -	NA (e)	NA (e)
2,5-Dichloro-3-acetylthiophene	H	180-181	$C_{14}H_9Cl_2NSO_3$	49.14 49.00	2.65 2.90	- -	NA (e)	NA (e)
2-Acetylpyrrole	H	174-176 (k)	$C_{14}H_{12}N_2O_3$	65.62 65.53	4.72 4.70	10.93 10.90	300	600 (e)
1-Methyl-2-acetyl-pyrrole	H	204-205	$C_{15}H_{14}N_2O_3$	66.65 66.62	5.22 5.26	10.36 10.36	NA (e)	NA (e)
3-(Me$_2$N-CH$_2$CH$_2$CO) indole	H	139-180	$C_{21}H_{21}N_3O_3$	69.40 69.25	5.82 5.89	11.56 11.33	600 (j)	NA (e)
4-Acetyl-5-methyl-1-phenylpyrazole	H	210-211	$C_{20}H_{17}N_3O_3$	69.15 68.44	4.93 4.95	12.10 11.69	NA (e)	NA (e)
2-Acetylpheno-thiazine	H	205-206	$C_{22}H_{16}N_2O_3S$	68.02 67.68	4.15 4.24	7.21 7.02	NA (e)	NA (e)
2-Acetylpheno-thiazine	1-C$_6$H$_5$-CH$_2$	158-158 (im)	$C_{29}H_{22}N_2O_3S$	72.78 72.73	4.63 4.58	- -	NA (e)	NA (e)

(a) Recrystallized from ethanol, mp uncorrected, spectral data consistent with structure. (b) Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed. MES = Maximal electroshock seizure test and Met = Pentylenetetrazol seizure threshold test. (c) Described in reference (1). (d) No activity at 300 mg/Kg. (e) No activity at 600 mg/Kg. (f) Reported (4) mp 207-208°. (g) MES ED_{50} 66.68, Met ED_{50} 114.06, TD_{50} 187.02. (h) MES ED_{60} 83.39, TD_{50} 491.84. (i) First prepared by Hossein Pajouhesh (5). (j) Recrystallized from ethyl acetate. (k) Reported (4) mp 275-276°. (k) Reported (4) mp 275-276°. (l) Some toxicity at this dose. (m) Recrystallized from benzene-ethyl acetate. (n) MES ED_{50} 98.07, TD_{50} 388.71. (o) MES ED_{50} 126.20, Met ED_{50} 514.94, TD_{50} 555.75.

Table II

Dehydration of Compounds from Table I



R	Mp °C (a)	Formula	Analysis Calcd. / Found C	H	N
2-Furyl	198-199	$C_{14}H_9NO_3$	70.29	3.79	5.86
			70.30	3.81	5.87
2-Thiophenyl	176-177	$C_{14}H_9NO_2S$	65.86	3.55	-
			66.08	3.62	-
2-Phenylthiazinyl	200-201 (b)	$C_{29}H_{20}N_2O_2S$	75.63	4.38	6.96
			75.20	4.43	7.03

(a) Recrystallized from ethanol, mp uncorrected, spectral data consistent with structure. (b) First prepared by Hossein Pajouhesh (5).

REFERENCES AND NOTES

(1) F. D. Popp and B. D. Donigan, *J. Pharm. Sci.*, **68**, 519 (1979).

(2) F. D. Popp, R. Parson, and B. E. Donigan, *ibid.*, **69**, 1235 (1980).

(3) Anticonvulsant screenings were carried out through the ADD program of the NINCDS, NIH. The standard screening protocol of that group was followed. We thank them for making this service available.

(4) N. Maxim and S. Petrascu, *Compt. Rend. Acad. Sci. Roumanie*, **8**, 65 (1946).

(5) Hossein Pajouhesh, M. S. Thesis, University of Missouri-Kansas City, 1981.