1-(1-Indanyl)- and 1-(1-Tetralyl)imidazole-5-carboxylate Esters, a Novel Type of Antifungal Agents

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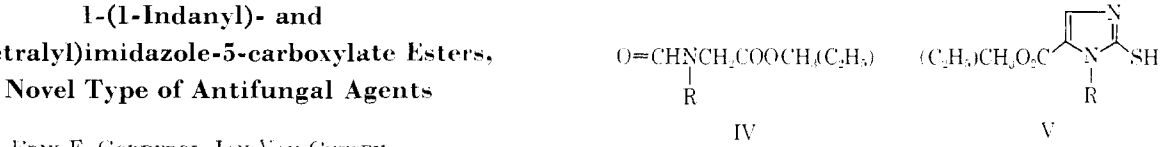
Received March 18, 1967
Revised Manuscript Received June 12, 1967

Recent reports from our laboratories described the synthesis, physical properties, and hypnotic activity of a number of DL-1-(1-arylalkyl)imidazole-5-carboxylic acid esters (I) as well as the preparation of cyclic variants of type II.[1,2] While pursuing this work further we had also occasion to prepare analogs in which the N substituent consisted of a 1-indanyl- or 1-tetralyl group, *i.e.*, type IIIa and b. Whereas the latter proved to be essentially devoid of hypnotic activity, they were shown, unexpectedly, to exhibit excellent antifungal properties. We wish to report here the synthesis and preliminary antifungal evaluation of these agents.



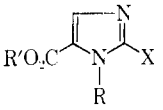
I II IIIa, $x=1$ b, $x=2$

IV V

a, R = 1-indanyl
b, R = 1-tetralyl

Chemistry.—The new compounds in question are listed in Table I. They were obtained by the Claisen formylation of the appropriately substituted N-formylglycine esters (IVa,b) followed by treatment of the formed enolate with HCl–HNCS. The resulting 2-mercaptoimidazole (Va,b) was then desulfurized and converted to the desired other esters (III) *via* the acid and acid chloride.

TABLE I
1-(1-INDANYL)- AND 1-(1-TETRALYL)-5-IMIDAZOLE CARBOXYLATES



Compd	X	R	R′	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	SH	1-Indanyl	CH_3	161–162	$C_{14}H_{14}N_2O_2S$	61.31	5.15	10.21	61.36	5.17	10.28
2	H	1-Indanyl	CH_3	154–155	$C_{14}H_{14}N_2O_2 \cdot HNO_3$	55.08	4.95	13.77	55.03	4.90	13.77
3	H	1-Indanyl	H	210–211	$C_{13}H_{12}N_2O_2$	68.41	5.30	12.28	68.10	5.14	12.38
4	H	1-Indanyl	C_2H_5	142–143	$C_{15}H_{16}N_2O_2 \cdot HNO_3$	56.42	5.37	13.16	56.07	5.36	13.05
5	SH	1-Tetralyl	C_2H_5	156–157	$C_{16}H_{18}N_2O_2S$	63.56	6.00	9.26	63.29	5.88	9.07
6	H	1-Tetralyl	C_2H_5	136–137	$C_{16}H_{18}N_2O_2 \cdot HNO_3$[a]	57.65	5.75	12.61	57.70	5.72	12.46
7	H	1-Tetralyl	H	220–221	$C_{14}H_{14}N_2O_2$	69.40	5.84	11.56	69.54	5.84	11.80
8	H	1-Tetralyl	CH_3	156–157	$C_{15}H_{16}N_2O_2 \cdot HNO_3$[b]	56.42	5.37	13.16	56.40	5.23	12.99
9	H	1-Tetralyl	*n*-C_3H_7	106–107	$C_{17}H_{20}N_2O_2 \cdot HNO_3$	58.75	6.09	12.10	59.00	6.08	11.96
10	H	1-Tetralyl	*i*-C_3H_7	142–143	$C_{17}H_{20}N_2O_2 \cdot HNO_3$	58.75	6.09	12.10	58.43	6.08	12.05
11	H	1-Tetralyl	*n*-C_4H_9	131–132	$C_{18}H_{22}N_2O_2 \cdot HNO_3$	59.82	6.42	11.63	59.99	6.20	11.38
12	H	1-Tetralyl	*i*-C_4H_9	140–141	$C_{18}H_{22}N_2O_2 \cdot HNO_3$	59.82	6.42	11.63	59.70	6.38	11.39
13	H	1-Tetralyl	*n*-C_5H_{11}	108–109	$C_{19}H_{24}N_2O_2 \cdot HNO_3$	60.78	6.71	11.19	60.82	6.73	11.30
14	H	1-Tetralyl	$CH_3CHCH_2CH(CH_3)_2$	134–135	$C_{19}H_{24}N_2O_2 \cdot HNO_3$	61.68	6.99	10.79	61.78	6.89	10.68
15	H	1-Tetralyl	$CH_2CH{=}CH_2$	102–103	$C_{17}H_{18}N_2O_2 \cdot HNO_3$	59.12	5.55	12.17	58.95	5.47	12.21
16	H	1-Tetralyl	$CH_2CH_2OCH_3$	124–125	$C_{17}H_{20}N_2O_3 \cdot HNO_3$	56.19	5.83	11.57	56.12	5.62	11.54
17	H	1-Tetralyl	$CH_2CH_2OC_2H_5$	120–121	$C_{18}H_{22}N_2O_3 \cdot HNO_3$	57.28	6.14	11.14	57.01	6.07	10.95
18	H	1-Tetralyl		116–118	$C_{19}H_{22}N_2O_3 \cdot HNO_3$	58.60	5.95	11.63	58.81	5.89	11.78
19	H	1-Tetralyl	C_6H_{11}	148–149	$C_{20}H_{24}N_2O_2 \cdot HNO_3$	62.00	6.50	10.85	61.88	6.41	10.68
20	H	1-Tetralyl	$CH_2C_6H_5$	134–135	$C_{23}H_{20}N_2O_2 \cdot HNO_3$	63.78	5.35	10.63	63.84	5.38	10.56

[a] Melting point of base, 91–92°. [b] Melting point of base, 64–65°.

Experimental Section

The imidazoles in question have been compiled in Table I. They were prepared essentially according to methods described earlier,[1] and no unusual difficulties were encountered. The synthesis and physical properties of the starting materials are briefly offered below.

N-(1-Indanyl)-N-formylglycine Methyl Ester (IVa).—The reaction of 63 g (0.47 mole) of 1-indanamine and 55 g (0.55 mole) of methyl chloroacetate in 200 ml of DMF containing 58 g (0.58 mole) of triethylamine gave crude substituted glycine ester. Upon formylation of the latter by means of excess formic acid in xylene, 42 g (39%) of product, mp 62–64°, was obtained. An analytical sample, prepared from isopropyl ether, melted at 71–72°.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.67; H, 6.49; N, 5.87.

N-(1-Tetralyl)-N-formylglycine ethyl ester (IVb) was prepared analogously to IVa in 62% yield. An analytical sample from isopropyl ether had mp 93–94°.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.70; H, 7.27.

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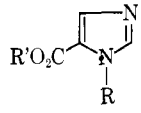
Antifungal Properties.—The fungistatic assay was carried out in Sabouraud's liquid (1 g of neopeptone Difco and 2 g of glucose Difco per 100 ml of distilled water) in 16 × 160 mm test tubes, each containing 4.5 ml of liquid medium which had been autoclaved at 120° for 15 min. The compounds to be tested were dissolved in 50% alcohol at initial concentration of 20 mg/ml. The solutions were subsequently diluted with sterile distilled water to give a concentration of 10 mg/ml. Successive decimal dilutions were made in distilled water. To tubes containing 4.5 ml of Sabouraud's liquid medium 0.5 ml of the solution of the drug was added, thereby obtaining concentrations of 1000, 500, 100, 10, and 1 μg/ml of medium. Control tubes were prepared by adding 0.5 ml of distilled water to 4.5 ml of medium, alcohol being added to give concentrations identical with the tubes containing 1000 and 500 μg of the drug. The filamentous fungi were incubated in Sabouraud's agar at 25° for 2–3 weeks. A block of 2 × 2 × 2 mm was then inoculated into the medium. All cultures were made in duplicate and were incubated at 25° for 14 days. Readings were then taken and were expressed as + if inhibition at the 100-μg/ml level was complete and as ++ if total inhibition occurred at 10 μg/ml.

Results

The results are summarized in Table II. Clearly, compounds of type IIIa,b exhibit excellent fungistatic activity against several organisms. Optimum effect is achieved with lower esters **6** and **9**. Lengthening of the chain results in diminished activity, notably against

TABLE II
ANTIFUNGAL ACTIVITIES



			Lowest level of inhibition[a]		
Compd	R	R′	*M. canis*	*T. mentagrophytes*	*T. rubrum*
2	1-Indanyl	CH_3	+	+	+
4	1-Indanyl	C_2H_5	+	++	++
8	1-Tetralyl	CH_3	+	+	++
6	1-Tetralyl	C_2H_5	++	++	++
9	1-Tetralyl	n-C_3H_7	++	++	++
10	1-Tetralyl	i-C_3H_7	+	+	+
11	1-Tetralyl	n-C_4H_9	+	++	++
12	1-Tetralyl	i-C_4H_9	+	++	++
13	1-Tetralyl	n-C_5H_{11}	0	+	+
14	1-Tetralyl	$CH_3CHCH_2CH(CH_3)_2$	0	0	0
15	1-Tetralyl	$CH_2CH{=}CH_2$	+	++	++
16	1-Tetralyl	$CH_2CH_2OCH_3$	+	++	++
17	1-Tetralyl	$CH_2CH_2OC_2H_5$	+	+	++
18	1-Tetralyl		+	+	+
19	1-Tetralyl	C_6H_{11}	0	0	++
20	1-Tetralyl	$CH_2C_6H_5$	0	0	++

[a] Total inhibition at 100 μg, +; at 10 μg, ++.

Microsporum canis. Chain interruption, in one case, (**13** *vs.* **17**) increases activity. The introduction of bulky groups causes greatly diminished inhibition (*i.e.*, **18–20**), while carboxylic acids **3** and **7** are totally inactive.

For comparative purposes sodium undecalenate, diamthazole,[3] and chlormidazole[4] were assayed concurrently against *M. canis*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*. None of these caused total inhibition below the 100-μg/ml level. One of our compounds, 1-(1-tetralyl)imidazole-5-carboxylic acid ethyl ester (**6**, proposed generic name, ethonamidate) has been selected for clinical evaluation. A more detailed pharmacological study of ethonamidate will be presented elsewhere.[5]

Acknowledgment.—We are indebted to Mr. J. Dockx for the preparation of starting materials and to Messrs. A. Sels and W. Verkest for the analytical determinations reported herein. Financial support of the Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw is gratefully acknowledged.

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(4) Polycid® (Grünenthal GmbH).
(5) R. Vanbreuseghem, J. Van Cutsem, and D. Thienpont, *Chemotherapia*, in press.

Lincomycin. VII. 4′-Depropyl-4′-ethoxylincomycins

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Received March 23, 1967

Variation in the length of the 4′-alkyl substituent of the antibiotic lincomycin (**1**) produced a series of analogs, some of which possessed enhanced antibacterial activity.[1] This note describes the synthesis and antibacterial activity of 4′-depropyl-4′-ethoxylincomycin (**3**) and its *cis* isomer **4**. These compounds may be classified as classical bioisosteres[2] of lincomycin and its *cis* isomer **2** in which the methylene adjacent to the proline ring in the 4′-propyl substituent is replaced by oxygen.

1-Carbobenzoxy-4-hydroxy-L-proline[3] was converted to the benzyl ester (**6**) and the latter etherified by the excellent method of Kuhn,[4] to form crude **7** in almost quantitative yield. Hydrogenolysis of **7** afforded 4-ethoxy-L-proline (**8**) as well as a small amount of the diketopiperazine **15**. Reductive methylation of **8** proceeded smoothly yielding **9**. Condensation of 1-methyl-4-ethoxy-L-proline (**9**) with methyl thiolincosaminide[5] using the mixed-anhydride procedure led to crystalline 4′-depropyl-4′-ethoxylincomycin (**3**).

In a similar manner, 1-carbobenzoxy-4-*cis*-hydroxy-L-proline[3] was converted to 1-methyl-4-*cis*-ethoxy-L-proline (**14**) and then to 4′-depropyl-4′-*cis*-ethoxylincomycin (**4**). In **4** the ethoxy substituent at C-4′ is oriented *cis* to the L-amide group, the same configuration as *cis*-lincomycin.[1]

4′-Depropyl-4′-ethoxylincomycin (**3**) and 4′-depropyl-4′-*cis*-ethoxylincomycin (**4**) have about 2% the activity of lincomycin when assayed in the standard-curve assay against *Sarcina lutea*.[6] Both compounds were inactive when administered subcutaneously at

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(2) V. B. Schatz in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 75.
(3) A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957).
(4) R. Kuhn, H. Trischmann, and I. Löiv, *Angew. Chem.*, **67**, 32 (1955).
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