Notes

Synthesis of 1- and 2-Substituted Indazoles as Anthelmintic Agents†

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Selective syntheses of 1- and 2-acyl-, alkoxycarbonyl-, and carbamoylindazoles are described. Spectroscopic data which were the basis for structural assignments are presented. These compounds, particularly methyl 2*H*-indazole-2-carboxylate and *N*-heptyl-*N*-methyl-2*H*-indazole-2-carboxamide, lack the spectrum of anthelmintic activity of the benzimidazole and benzotriazole anthelmintics to which they are structurally related.

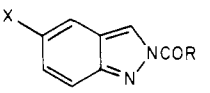
The anthelmintics with the broadest known spectra of activity are benzimidazoles.[1] Benzotriazoles with 1- and 2-carbamoyl substituents are also reported to have broad-spectrum anthelmintic activity.[2] As part of our anthelmintic research program we were interested in the anthelmintic potential of the indazole nucleus. This report describes the preparation of a series of 1- and 2-substituted indazoles 1–11.

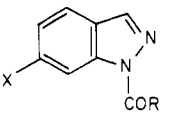
The general method used in preparing the desired compounds involved addition of an acid chloride, chloroformate, or carbamoyl chloride to an indazole in the presence of an amine such as pyridine or triethylamine. Since reaction may lead to substitution at either nitrogen, selective synthetic methods were required. The literature indicates that acylation of indazoles at low temperature leads to predominant substitution at the 2 position while reaction at slightly higher temperature leads to predominant substitution at the 1 position.[3-5] We found that the 2-isomer **1** could be prepared by reaction of methyl chloroformate with indazole at −78° and the 1-isomer **2** generated from the same reaction at room temperature. However, even at room temperature, reaction of indazole with benzyl chloroformate or 2-furoyl chloride gave only 2-isomers **3** and **5**. This implies that steric factors are also important in determining the stereochemical outcome of these reactions. The 1-(2-furoyl) isomer **6** was prepared from indazole sodium salt and 2-furoyl chloride.

Indazole failed to react with *N*-heptyl-*N*-methylcarbamoyl chloride at 27° but reaction did proceed in refluxing toluene to give the 2-isomer **7** with only trace amounts of the 1-isomer being formed. The 1-isomer **8** was prepared by reaction of indazole with phosgene to give 1,1'-carbonyldiindazole, followed by the addition of *N*-heptyl-*N*-methylamine.

The syntheses of 2-isomers **1** and **3** were previously reported[6] by reaction of indazole with the corresponding chloroformate at reflux or from indazole silver salt and chloroformate in ether. However, these structural assignments were made without the benefit of spectroscopic evidence and the products of these reactions are, in fact, 1-isomers **2** and **4**.

Structural assignments were made on the basis of the relative chemical shift difference of the C_3 proton signal.[5,7,8] Substitution at the 2 position results in a downfield shift of the C_3 proton signal whereas substitution at the 1 position has little effect on the chemical shift of this proton. Analogously the C_7 proton signal is shifted by 1-substitution but not by 2-substitution (see Table I).



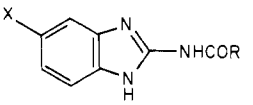


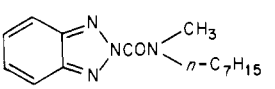
1, R = OCH_3; X = H
3, R = $OCH_2C_6H_5$; X = H
5, R = 2-furyl; X = H
7, R = $N(CH_3)$-*n*-C_7H_{15}; X = H
9, R = quinoxalin-2-yl; X = H
11, R = $N(CH_3)$-*n*-C_6H_{13}; X = Cl

2, R = OCH_3; X = H
4, R = $OCH_2C_6H_5$; X = H
6, R = 2-furyl; X = H
8, R = $N(CH_3)$-*n*-C_7H_{15}; X = H
10, R = $N(CH_3)$-*n*-C_6H_{13}; X = NO_2

Discussion

Several benzimidazoles possessing a broad spectrum of anthelmintic activity against the intestinal nematodes of sheep have been reported. Similar activity has been reported for certain benzotriazoles.[2] We were interested to see if structurally related compounds containing the indazole nucleus would have comparable activity.





12a, X = H; R = OCH_3
b, X = *n*-C_4H_9; R = OCH_3
c, X = H; R = $N(CH_3)$-*n*-C_7H_{15}
d, X = H; R = 2-furyl

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Compound **12b** (parbendazole) is highly active against both the enteral phase of *Trichinella spiralis* in mice[10] and a broad spectrum of intestinal nematodes in sheep.[11] Benzimidazoles **12a** and **12d**[12] are active in sheep at 25 mg/kg po but are not active against *T. spiralis* at this dose level. Several indazoles showed some activity against *T. spiralis* in mice but none tested demonstrated activity against sheep nematodes. Another benzimidazole bearing the side chain of the benzotriazole, **12c**, was inactive in both tests. The available data indicated the indazole nucleus to be less attractive than the benzimidazole nucleus for the preparation of new anthelmintics.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were determined with a Varian Associates T-60 spectrometer. Uv spectral data are given in Table II.

† Dedicated to the memory of Professor Edward Smissman.

Table I. Physical Properties and NMR Spectra

No.	Mp, °C	Yield, %[a]	Formula[b]	NMR[c] δ H_3	NMR[c] δ H_7	% redn of *T. spiralis*, 25 mg/kg po + sc[d]	Act. against intestinal nematodes in sheep, % redn
1	85-87	82.5	$C_9H_8N_2O_2$	8.62	7.67	26	
2	58-60[g]	57	$C_9H_8N_2O_2$	8.14	8.16	23	
3	97-99	76	$C_{15}H_{12}N_2O_2$	8.66	7.7	74	0[e]
4	81.5-82.5[h]	83	$C_{15}H_{12}N_2O_2$	8.20	8.30		
5	110-111	82.5	$C_{12}H_8N_2O_2$	8.90		58	0[e]
6	109-110	78	$C_{12}H_8N_2O_2$	8.15	8.55	16	0[e]
7	Liquid	52.5	$C_{16}H_{23}N_3O$	8.57	7.67	45	0[e]
8	Liquid	42	$C_{16}H_{23}N_3O$	8.07	8.07		
9	168-170	50	$C_{16}H_{10}N_4O$	9.36[i]	8.50[i]	36	
10	59.5-61	33	$C_{15}H_{20}N_4O_3$	9.0	8.0	41	
11	66-67.5	30	$C_{15}H_{20}ClN_3O$	7.61	7.0	40	
12a			$C_9H_9N_3O_2$			0	98[f]
12b			$C_{13}H_{17}N_3O_2$			99	99[f]
12c			$C_{16}H_{24}N_4O$			14	0[e]
12d			$C_{12}H_9N_3O_2$				99[f]
13			$C_{15}H_{22}N_4O$				Active[j]

[a] Yields not maximized. [b] Analyses for C, H, and N were obtained for all compounds and were within ±0.3% of the theoretical values. [c] Solvent was $CDCl_3$ unless otherwise noted. [d] Mice infected with 250 infective larvae of *T. spiralis* were dosed with 25 mg/kg po plus 25 mg/kg sc 8 h postinfection. See ref 10. [e] Dose 15 mg/kg. Sheep naturally parasitized with a variety of intestinal nematodes were dosed orally with drug and nematode eggs per gram of feces determined 7 days after dosing and compared with pretreatment egg counts: N. R. Stoll, *Parasitology*, **22**, 116 (1930). [f] Dose 25 mg/kg. Percentage reduction of intestinal nematode burden: H. E. Moskey and P. D. Harwood, *Am. J. Vet. Res.*, **2**, 55 (1941). [g] Lit.[6] mp 59-60°. [h] Lit.[6] mp 83-84°. [i] Solvent was Me_2SO-d_6. [j] Reference 2.

Table II. Ultraviolet Spectral Data[a,b]

2-Isomers No.	2-Isomers Max, nm (ε)	1-Isomers No.	1-Isomers Max, nm (ε)
1	278 (8590), 289 (9300)	2	246 (9040), 252 (8080), 288 (5560), 297 (5120)
3	279 (8420), 290 (9100)	4	246 (11 500), 253 (10 400), 288 (7200), 298 (6720)

[a] Solvent EtOH, 95%. [b] For comparison, see ref 9.

General Procedure. To 2.36 g (20 mmol) of indazole dissolved in 75 ml of dry acetone was added 2.4 g (30 mmol) of pyridine (other amine bases such as triethylamine are also suitable) and cooled in a dry ice–acetone bath (cooling is not necessary if the 1-isomer is desired). A solution of 30 mmol of acylating reagent in 40 ml of dry acetone was added dropwise. After addition was complete the mixture was warmed to room temperature (3 h), pyridine hydrochloride filtered, and the acetone evaporated in vacuo. Solids generally were recrystallized from heptane (an exception was 1 which rearranged to 2 on heating in heptane).

1-(2-Furanylcarbonyl)-1*H*-indazole (6). To 2.3 g (20 mmol) of indazole dissolved in 100 ml of dry THF and cooled to 0° was added 0.85 g (20 mmol) of sodium hydride (57% oil dispersion). After hydrogen evolution ceased, 3.9 g (30 mmol) of 2-furoyl chloride dissolved in 30 ml of dry THF was added dropwise and the mixture stirred 2.5 h. The solvent was evaporated and the resulting oil diluted with 200 ml of ether and washed with dilute HCl (3 × 100 ml), saturated $NaHCO_3$ (3 × 100 ml), and water (3 × 150 ml), and dried ($MgSO_4$). Evaporation of the ether and recrystallization from heptane gave 3.3 g (78%) of **6** as yellow needles, mp 109–110°.

***N*-Heptyl-*N*-methyl-1*H*-indazole-2-carboxamide (7).** A mixture of 2.45 g (29.2 mmol) of indazole, 5.58 g (29.2 mmol) of *N*-heptyl-*N*-methylcarbamoyl chloride, and 3.16 g (40 mmol) of pyridine in 100 ml of toluene was refluxed for 24 h. The toluene was evaporated, and the residue was treated with ether, washed with water (3 × 300 ml), dilute HCl (3 × 200 ml), and saturated $NaHCO_3$ (2 × 100 ml), and dried ($MgSO_4$). Evaporation of the ether gave a yellow oil which was purified by chromatography on silica gel using ethyl ether–petroleum ether (1:1) to give 4.2 g (52.5%) of **7** as a slightly yellow oil: $n^{25}D$ 1.5449.

***N*-Heptyl-*N*-methyl-1*H*-indazole-1-carboxamide (8).** To a solution of 1.94 g (20 mmol) of phosgene in 50 ml of ethyl ether (a solution of 12.5% phosgene in benzene was used) at 0° was added 2.36 g (20 mmol) of indazole dissolved in 150 ml of ether containing 1.5 g (20 mmol) of pyridine. After addition was complete the reaction mixture was stirred for 1 h at 0° and 1 h at 27°. The resulting precipitate was rapidly separated and 5.16 g (40 mmol) of *N*-heptyl-*N*-methylamine in 40 ml of ether was added dropwise to the filtrate at room temperature over a 50-min period. After stirring 2 h at room temperature, the mixture was filtered and the ethereal solution was washed with water (3 × 100 ml), dilute HCl (3 × 100 ml), and saturated $NaHCO_3$ (2 × 100 ml) and dried ($MgSO_4$). Evaporation of the ether gave a yellow oil which was purified by chromatography on silica gel using benzene to give 2.3 g (42%) of **8** as a pale yellow oil, $n^{25}D$ 1.4506, and shown to be different from the 2-isomer **7** by NMR.

***N*-Hexyl-*N*-methyl-6-nitro-1*H*-indazole-1-carboxamide (10).** To 1.63 g (20 mmol) of 6-nitroindazole in 60 ml of dry THF at 0° was added 0.95 g of 57% NaH (oil dispersion). After hydrogen evolution ceased 1.75 g (20 mmol) of *N*-hexyl-*N*-methylcarbamoyl chloride was added in one portion. The ice bath was removed and the mixture warmed to room temperature and treated with 10 ml of water. The THF was evaporated and the residue partitioned between ethyl ether and 0.1 N KOH. The ether layer was separated, washed with water (2 × 100 ml), and dried (K_2CO_3). Evaporation gave an amber oil which solidified on standing. Recrystallization from ethyl ether–petroleum ether gave 2.0 g (33%) of **10** as an off-white solid: mp 59.5–61.5°.

References and Notes

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