

Salvatore Plescia, Giuseppe Daidone and Vincenzo Sprio

Istituto di Chimica Farmaceutica, Facoltà di Farmacia, Via Archirafi, 32, 90123 Palermo, Italy

Received October 12, 1978

The reactivity of some indole derivatives towards the semicarbazone of ω -bromoacetophenone has been reported. Substituents at position 1 and 2 of the indole ring greatly affect the course of the reaction. 1,4,4a,9a-Tetrahydro-9H-pyridazino[3,4-*b*]indole derivatives or 3-indolyl derivatives were obtained depending on the substituents. The structures were assigned on the basis of satisfactory analytical and spectroscopic data.

J. Heterocyclic Chem., **16**, 805 (1979).

In the course of our studies on condensed pyridazine derivatives, we have reported the successful application of the reaction of the semicarbazone of ω -bromoacetophenone with *N*-methylindole to the preparation of the tricyclic system, pyridazino[3,4-*b*]indole (1).

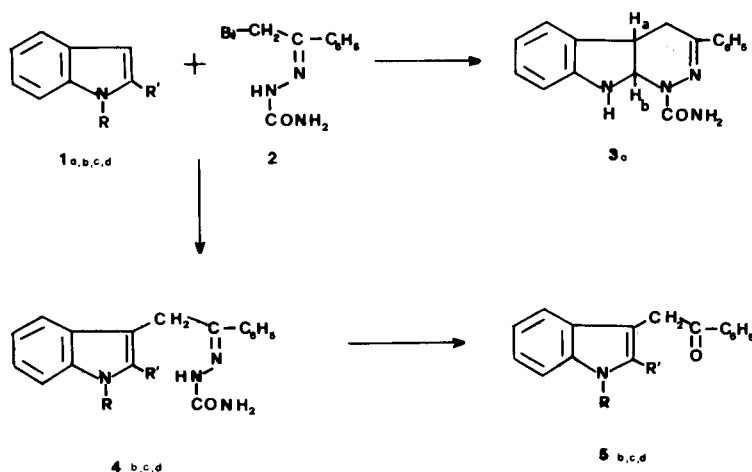
We now report the results of our attempts to extend the reaction by using some indole derivatives as starting materials. We found that the reaction of the unsubstituted indole **1a** with **2** in refluxing chloroform in the presence of triethylamine afforded, together with a considerable amount of starting indole and tarry material, several products which were monitored by thin layer chromatography. Work-up and column chromatography showed one product to be the desired 1-carbamoyl-3-phenyl-9H-1,4,4a,9a-tetrahydropyridazino[3,4-*b*]indole (**3a**), obtained in a very low yield.

The nmr spectrum exhibited the signals related to the aromatic protons and also those signals consistent with the methylene protons at 2.80 δ and with the two *cis* H_A,H_B protons, which showed a coupling constant of 7.5 Hz. Moreover, the H_B-proton appeared as a pair of doublets centered at δ 5.72 and with a $J_{\text{NH},\text{H}_B} = 3.0$ Hz. The

ir spectrum confirmed the presence of the NH and NH₂ groups in the 3 μ region and of the carbonyl group at 1680 cm^{-1} .

We observed that indole derivatives with the 3-position free, the 1-position free or substituted and the 2-position carrying a methyl or a phenyl group afforded only the semicarbazones **4b,c,d** (see Scheme). These results are consistent with normal electrophilic substitution occurring largely at the 3-position in indole derivatives with the C-3 position unsubstituted. It seems likely that the substituents at the 2-position produced steric effects, clearly indicating that these groups hindered the attack of the nitrogen atom of the semicarbazone chain on the C-2 position preventing the formation of the pyridazine nucleus.

Indole derivatives with the 3-position free, the 1-position free or substituted and the 2-position carrying an ester group; e.g., 1-methyl-2-carbethoxyindole and 2-carbomethoxyindole did not react. In these substrates apart the possible steric hindrance, the electron-withdrawing effects of the ester group were very effective and the 3-position became less reactive towards such a weak electrophile as compound **2**.



(a) R = R' = H ; (b) R = H, R' = CH₃ ; (c) R = H, R' = C₆H₅ ; (d) R = R' = CH₃

The structures of the semicarbazones of 3-phenacylindoles **4b,c,d** were consistent with their ir and nmr spectra as well as the analytical data.

By action of sulphuric acid in ethanol, these compounds were readily transformed into the corresponding ketones **5b,c,d**. This sequence of reactions represents a facile synthetic route to 3-phenacylindoles, which are good intermediates for the preparation of compounds of biological importance.

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. The ir spectra were determined in Nujol mulls with a Perkin-Elmer Infracord 137 spectrophotometer; nmr spectra (DMSO- d_6) (unless otherwise specified) were obtained with a Jeol C-60 H spectrometer (TMS as internal reference). A 270 Perkin-Elmer mass spectrometer was employed for determination of low resolution 70 eV mass spectra.

1-Carbamoyl-3-phenyl-9H-1,4,4a,9a-tetrahydropyridazino[3,4-*b*]-indole (**3a**).

Indole **1a** (20 mmoles) was dissolved in dry chloroform (100 ml.) and 20 mmoles of the semicarbazone of ω -bromoaceto-phenone (**2**) was added. Triethylamine (20 mmoles) was added in one portion and the mixture was then refluxed for 1.5 hours. After cooling, the resultant solution was washed with water (2 x 100 ml.), dried (calcium chloride), mixed with silica gel (25 g.) and concentrated under reduced pressure to dryness. The resultant solid was chromatographed on a column (65 x 5 cm) of silica gel. Elution with cyclohexane-ethyl acetate (95:5) removed

unreacted indole (1.6 g.). The second eluate with ethyl acetate-cyclohexane (8:2) afforded tarry material; further elution with ethyl acetate gave 180 mg. of **3a** as white needles from ethanol, m.p. 203-205°; molecular weight by mass spectroscopy m/e 292; ir: cm^{-1} 3200-3300 (broad) 3380 and 3480 (NH, NH₂) 1680 (CO); nmr, δ : 2.80 (2H, pseudo-d, CH₂, $J \cong 6.0$ Hz) 3.65 (1H, a set of signals, H_A) 5.72 (1H, dd, H_B, $J_{HA,HB} \cong 7.5$

Hz and $J_{NH,H_B} = 3.0$ Hz) 6.20-8.00 (12H, a set of signals,

NH, NH₂, C₆H₅ and C₆H₅ and C₆H₄).

Anal. Calcd. for C₁₇H₁₆N₄O: C, 69.84; H, 5.52; N, 19.17. Found: C, 69.80; H, 5.48; N, 19.11.

3-Phenacylindole Semicarbazones **4b,c,d**

Triethylamine (10 mmoles) was added to a mixture of **2** (10 mmoles) and 10 mmoles of indoles **1b,c,d** dissolved in dry chloroform (100 ml.). After refluxing 1.5 hours, the solvent was removed under reduced pressure and 50 ml. of methanol-water (4:1) was added. After standing overnight the compounds **4**, as white crystalline products, were obtained and recrystallized from ethanol. These products are listed in the table.

3-Phenacylindoles **5b,c,d**.

A mixture of **4b,c,d** (2 mmoles), ethanol (15 ml.) and 1.2 ml. of 45% aqueous sulphuric acid was heated until the material was completely dissolved. The solution was refluxed for an additional 10 minutes. On cooling, the title compounds, described in the Table, were separated as a crystalline mass and recrystallized from ethanol.

REFERENCES AND NOTES

- (1) V. Sprio and S. Plescia, *Ann. Chim. (Rome)*, **61**, 655 (1971).

Table

1-R-2-R'-3-Phenacylindole Semicarbazone and 1-R-2-R'-3-Phenacylindole Derivatives

Compounds	R	R'	X	Yield %	M.p. °C	Formula	Analyses					
							Calcd.			Found		
							C	H	N	C	H	N
4b	H	CH ₃	=NNHCONH ₂	62	225-228	C ₁₈ H ₁₈ N ₄ O (a)	70.56	5.92	18.29	70.58	5.94	18.25
4c	H	C ₆ H ₅	=NNHCONH ₂	66	250-252	C ₂₃ H ₂₀ N ₄ O (b)	74.98	5.47	15.21	74.92	5.40	15.18
4d	CH ₃	CH ₃	=NNHCONH ₂	64	205-206	C ₁₉ H ₂₀ N ₄ O (c)	71.22	6.29	17.49	71.10	6.18	17.48
5b	H	CH ₃	O	70	108-109	C ₁₇ H ₁₅ NO (d)	81.90	6.06	5.62	81.79	6.00	5.54
5c	H	C ₆ H ₅	O	75	148-149	C ₂₂ H ₁₇ NO (e)	84.86	5.50	4.50	84.69	5.54	4.38
5d	CH ₃	CH ₃	O	74	106-108	C ₁₈ H ₁₇ NO (f)	82.10	6.51	5.32	82.11	6.50	5.36

(a) Ir, cm^{-1} : 3200-3300 (broad) 3460 (NH, NH₂) 1690 (CO); nmr, δ : 2.27 (3H, s, CH₃) 4.10 (2H, s, CH₂) 6.60 (2H, s, NH₂) 6.80-7.80 (9H, m, C₆H₄ and C₆H₅) 10.00 (1H, s, NH). (b) Ir, cm^{-1} : 3200-3320 (broad) 3460 (NH, NH₂) 1700 (CO); nmr, δ : 4.30 (2H, s, CH₂) 6.60 (2H, s, NH₂) 6.80-7.80 (14H, m, 2 x C₆H₅ and C₆H₄) 9.80 (1H, s, NH) 11.35 (1H, s, NH). (c) Ir, cm^{-1} : 3100-3200 (broad) 3460 (NH, NH₂) 1700 (CO); nmr, δ : 2.40 (3H, s, CH₃) 3.60 (3H, s, CH₃) 4.40 (2H, s, CH₂) 6.60 (2H, s, NH₂) 6.80-8.00 (9H, m, C₆H₅ and C₆H₄) 9.60 (1H, s, NH). (d) Ir, cm^{-1} : 3280 (NH) 1660 (CO); nmr, δ : 2.32 (3H, s, CH₃) 4.30 (2H, s, CH₂) 6.80-8.00 (9H, m, C₆H₅ and C₆H₄) 10.77 (1H, s, NH). (e) Ir, cm^{-1} : 3320 (NH) 1680 (CO); nmr, δ : 4.05 (2H, s, CH₂) 6.80-8.10 (14H, m, 2 x C₆H₅ and C₆H₄) 11.30 (1H, s, NH). (f) Ir, cm^{-1} : 1680 (CO); nmr (deuteriochloroform), δ : 2.40 (3H, s, CH₃) 3.60 (3H, s, CH₃) 4.40 (2H, s, CH₂) 6.80-8.20 (9H, m, C₆H₅ and C₆H₄).

