A New Procedure for the Cyclization of 2-Indole- and 3-Indolecarbohydrazones to 5*H*-Pyridazino[4,5-*b*]indole Derivatives

A. Monge Vega*, J. A. Palop, M. T. Martínez (1) and E. Fernández Alvarez* (2)

(1) Facultad de Farmacia de la Universidad de Navarra, Pamplona, Spain
(2)Instituto de Química Orgánica General del CSIC, Juan de la Cierva, 3, Madrid-6, Spain

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A new procedure for the cyclization of 2-indolecarbohydrazones (**5**) to 1,2,3,4-tetrahydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles (**6**) and for the cyclization of 3-indolecarbohydrazones (**7**) to 1-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indoles (**8** and **9**) is described. The hydrazones (**5** or **7**) were treated with an acyl halide (acetyl or benzoyl chlorides) and triethylamine in ethyl acetate of chloroform as solvents to give the compounds **6** (20-70%) from the compounds **5**, and the compounds **8** (20-60%) from the compounds **7**. Through refluxing with ethanol-hydrochloric acid the compounds **8a-8f** selectively separate the acetyl group on N^5 to give the respective compounds, **9a-9f**. The ir and ^{1}H-nmr spectra of all the compounds **5**, **6**, **7**, **8** and **9** and the uv, mass and ^{13}C-nmr spectra of the compounds **7h**, **7i**, **8h** and **8i** are discussed.

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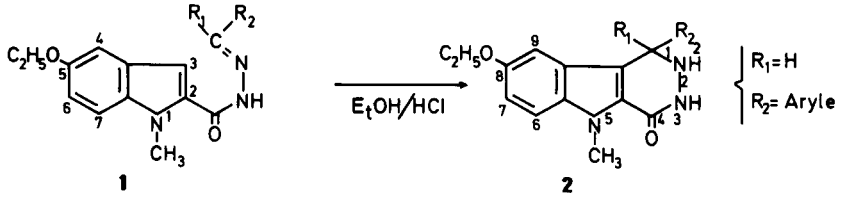
As a continuation of previous studies (1,2) on the cyclization of 2- (or 3)-indolecarbohydrazones to derivatives of 5*H*-pyridazino[4,5-*b*]indole, we describe here a new procedure for the cyclization of 2-indolecarbohydrazones to derivatives of 4-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole, and of the 3-indolecarbohydrazones to derivatives of 1-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole.

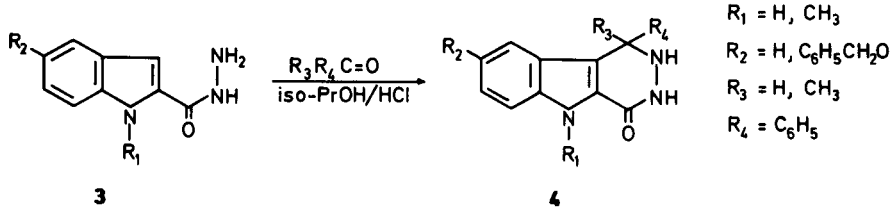
The derivatives of 5*H*-pyridazino[4,5-*b*]indole are generally obtained by any one of the following procedures: (a) cyclization with hydrazines of 3-acyl (3,4), 3-hydroxymethyl (4,5), 3-acetoxymethyl or 3-halomethyl (6) derivatives of indoles, with suitable substituents in position 2; 2-carbethoxyindoles are generally used, which leads to the 4-oxo derivatives; (b) condensation of 2-indolemethylhydrazines (7) or 3-indolemethylhydrazines (8) with aldehydes; (c) intramolecular reductive cyclization of 4-(*o*-nitrophenyl)pyridazines (9); (d) acid catalyzed intramolecular cyclization of 2-indolecarbohydrazones (1,10-13) or acid catalyzed condensation of 2-indolecarbohydrazides (2) with aldehydes or ketones.

We have already described (1) that the intramolecular cyclization of 2-indolecarbohydrazones (**1**, Scheme 1) with 12-14*N* hydrochloric acid in ethanol or dioxane leads (80%) to the respective derivatives of 4-oxo-5*H*-pyridazino-[4,5-*b*]indole (**2**), when R_1 = H and R_2 = aryl (C_6H_5, *p*-HO-C_6H_4), but the hydrazone **1** cleaves under those conditions to give the hydrochloride of 2-(1-methyl-5-ethoxyindole)carbohydrazide, when R_1 = H, CH_3 and R_2 = alkyl. On the other hand, the condensation of 2-indolecarbohydrazones (**3**, Scheme 2) with benzaldehyde or methyl ethyl ketone led satisfactorily (56-76%) to the correspond-

Scheme 1



Scheme 2



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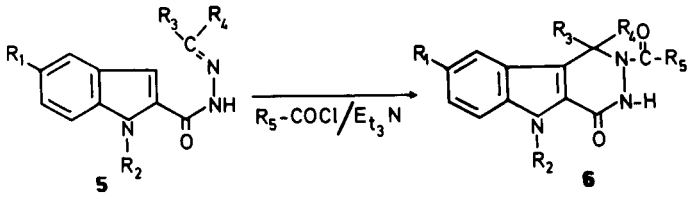
ing derivatives of the pyridazinoindole (**4**), even if the reaction failed with aliphatic aldehydes because they polymerize under those conditions.

Scheme 3



R_1= H, $C_6H_5CH_2O$
R_2= H, CH_3
R_3= H, CH_3
R_4= Aryle

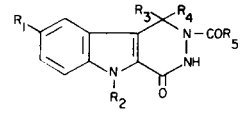
R_1= H, $C_6H_5CH_2O$
R_2= H, CH_3-CO; C_6H_5CO
R_3= H, CH_3
R_4= Aryle
R_5= CH_3; C_6H_5

In this paper a new method is described, which seems to be a general one, for the cyclization of 2-indolecarbohydrazones (**5**, Scheme 3) to derivatives of 4-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (**6**) and the cyclization of 3-indolecarbohydrazones (**7**, Scheme 4) to derivatives of 1-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino-[4,5-*b*]indole (**8** and **9**), for the treatment of the corresponding carbohydrazones with an acyl halide (acetyl or benzoyl chlorides) and triethylamine in ethyl acetate or chloroform, respectively, as solvents. The reaction was carried out at a temperature below 40°, by slow and gradual addition of the acyl halide (40-70 mmoles) to solutions or suspensions of the carbohydrazides (3 mmoles) in the solvent mentioned above containing triethylamine. The reaction takes place in about 0.5-3 hours with the total dissolution of the products and the formation of a precipitate.

From the 2-indolecarbohydrazones (**5**, Scheme 3) the compounds **6** (Table 1) were obtained in acceptable yields (20-70%). The reaction supposes the formation of the pyridazine derived ring, the acylation on N^2 of the same and, in this case, also of the pyrrole N^1. All of the compounds showed correct elemental analysis and satisfactory ir and ^{1}H-nmr spectra, which will be discussed later. In a similar way, the 3-indolecarbohydrazones (**7**, Scheme 4) led satisfactorily (20-60%) to the derivatives **8** (Table 2). The reaction involves the cyclization with the formation of the pyridazine derived ring and the acylation on N^3 and, in this case, on N^5 of the pyridazinoindole system. The acetyl group on N^5 in compounds **8** was very labile and it was easily removed when the recrystallization of the products from ethanol was attempted. For this reason satisfactory elemental analysis for the compounds **8a-8f** were not obtained, even though they gave ir and ^{1}H-nmr spectra supporting the proposed structures. However, the benzoyl derivatives **8g-8i** were stable and they could be recrystallized.

Through refluxing with ethanol containing traces of hydrochloric acid the compounds **8a-8f** selectively separate the acetyl group on N^5 to give the respective com-

Table I

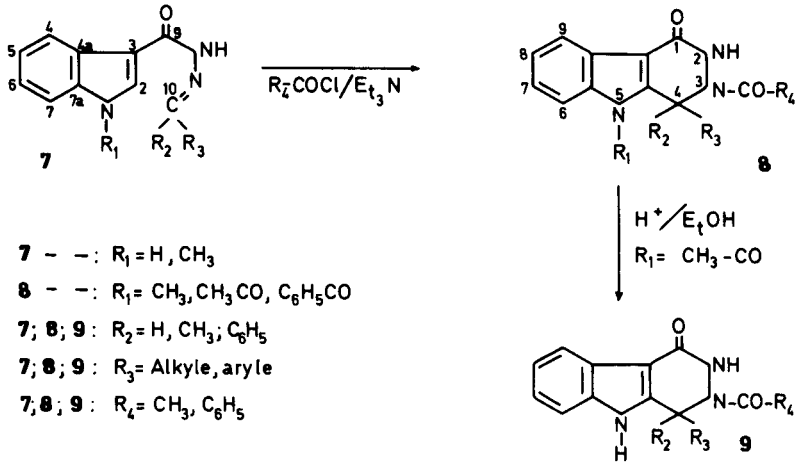


4-Oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indoles **6**

N°	R_1	R_2	R_3	R_4	R_5	Yield (%)	M.p. (a)	Formula (b)	Elemental Analysis, % Calcd. C	H	N	Found C	H	N
6a	H (c)	CH_3-CO	H	C_6H_5	CH_3	60	94-96	$C_{20}H_{17}N_3O_3$	69.15	4.93	12.10	69.31	5.05	12.04
6b	H	CH_3-CO	CH_3	C_6H_5	CH_3	40	139-141	$C_{21}H_{19}N_3O_3$	69.79	5.30	11.63	69.80	5.33	11.92
6c	H	CH_3-CO	H	(*p*)$CH_3C_6H_4$	CH_3	60	92-94	$C_{21}H_{19}N_3O_3$	69.79	5.30	11.63	69.79	5.00	11.86
6d	H	CH_3-CO	H	(*p*)$CH_3COOC_6H_4$	CH_3	50	117-118	$C_{23}H_{21}N_3O_5$	65.18	4.72	10.36	65.28	4.57	10.02
6e	H	CH_3-CO	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	60	126-128	$C_{21}H_{17}N_3O_5$	64.45	4.38	10.74	64.27	4.50	10.77
6f	H	CH_3	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	60	116-118	$C_{20}H_{17}N_3O_4$	66.11	4.72	11.56	65.92	4.65	11.61
6g	$C_6H_5CH_2O$	H	H	C_6H_5	CH_3	20	203-205	$C_{25}H_{21}N_3O_3$	72.98	5.14	10.21	73.34	5.37	10.23
6h	$C_6H_5CH_2O$	CH_3-CO	H	C_6H_5	CH_3	50	144-146	$C_{27}H_{23}N_3O_4$	71.51	5.11	9.17	71.49	5.21	8.96
6i	$C_6H_5CH_2O$	CH_3-CO	H	(*p*)ClC_6H_4	CH_3	40	175-177	$C_{27}H_{22}N_3O_4Cl$	66.46	4.52	8.61	66.05	4.70	8.79
6j	$C_6H_5CH_2O$	CH_3-CO	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	60	145-147	$C_{28}H_{23}N_3O_6$	67.70	4.66	8.45	67.72	4.47	8.61
6k	$C_6H_5CH_2O$	CH_3	H	C_6H_5	CH_3	40	160-161	$C_{26}H_{23}N_3O_3$	73.40	5.45	9.88	73.46	5.10	10.13
6l	$C_6H_5CH_2O$	CH_3	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	70	168	$C_{27}H_{23}N_3O_5$	69.07	4.94	8.95	69.05	5.24	8.92
6m	$C_6H_5CH_2O$	CH_3	H	$(CH_2)_5CH$	CH_3	65	114	$C_{28}H_{33}N_3O_3$	70.57	6.44	10.73	70.53	6.63	10.73
6n	H	H	H	C_6H_5	C_6H_5	50	173-175	$C_{25}H_{17}N_3O_3$	75.19	4.66	11.44	75.35	4.48	11.76
6o	H	CH_3	H	(*p*)$CH_3C_6H_4$	C_6H_5	60	130-132	$C_{26}H_{21}N_3O_3$	75.93	5.35	10.63	76.23	5.40	10.79
6p	H	CH_3	H	3,4-$(CH_2O_2)C_6H_3$	C_6H_5	60	150-152	$C_{26}H_{19}N_3O_5$	70.58	4.50	9.88	70.50	4.26	10.08
6q	H	C_6H_5CO	CH_3	C_6H_5	C_6H_5	20	223-225	$C_{30}H_{21}N_3O_3$	76.42	4.49	8.91	76.50	4.62	9.05
6r	H	C_6H_5CO	H	(*p*)$CH_3C_6H_4$	C_6H_5	50	200-201	$C_{31}H_{23}N_3O_3$	76.69	4.77	8.65	76.62	4.94	8.57

(a) Recrystallized from 2-propanol. (b) Satisfactory Ir and ^{1}H-nmr spectra were obtained for all the compounds. (c) Reported (11) m.p. 190-192°.

Scheme 4



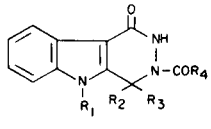
pounds **9a-9f**, both of which are stable. These could be recrystallized; the elemental analysis and the ir and ^{1}H-nmr spectra were satisfactory.

All the compounds described in Tables 1 and 2 are new, except compound **6a**, previously reported (11) by treatment of the compound **4** ($R_1 = R_2 = R_3 = H$, $R_4 = C_6H_5$) with acetic anhydride.

The ir spectra of the starting hydrazones **5** as well as of the pyridazinoindoles **6** are complex and some examples have already been comparatively commented on by us (1,2). Relative to the compounds which this paper refers to, we report in the Experimental the most significant data: compounds **5** show bands about 1625-1650 (s) and 1600-1620 (s) for the groups C=O and C=N, respectively; compounds **6** show bands about 1610-1690 (s), 1665-1730 (s) and 1690-1705 (s) assigned to the groups C^4=O,

Table 2

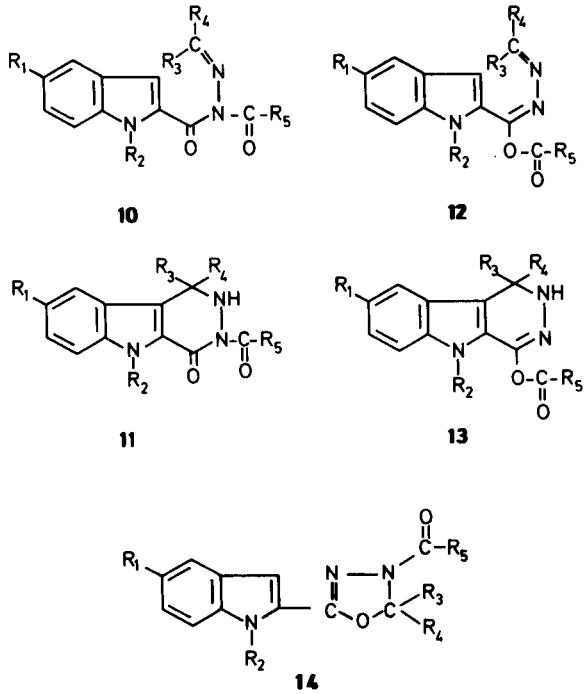
1-Oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indoles **8** and **9**



N°	R_1	R_2	R_3	R_4	Yield (%)	M.p. Solvent recrystallization	Formula (a)	Elemental Analysis, % Calcd. C	H	N	Found C	H	N
8a	CH_3-CO	CH_3	CH_3CH_2	CH_3	20	189-190 (b)	$C_{17}H_{19}N_3O_2$						
8b	CH_3-CO	CH_3-CH_2	CH_3CH_2	CH_3	40	143-145 (b)	$C_{18}H_{21}N_3O_2$						
8c	CH_3-CO	H	C_6H_5	CH_3	50	158-160 (b)	$C_{20}H_{17}N_3O_2$						
8d	CH_3-CO	H	(*p*)$CH_3C_6H_4$	CH_3	60	175-177 (b)	$C_{21}H_{19}N_3O_2$						
8e	CH_3-CO	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	60	167-169 (b)	$C_{21}H_{17}N_3O_4$						
8f	CH_3-CO	H	$CH_3(CH_2)_5CH_2$	CH_3	40	103-105 (b)	$C_{23}H_{31}N_3O_2$						
8g	C_6H_5-CO	H	(*p*)$CH_3C_6H_4$	C_6H_5	50	200-201 2-propanol	$C_{31}H_{23}N_3O_2$	76.69	4.77	8.65	76.62	4.94	8.57
8h	CH_3	H	C_6H_5	C_6H_5	70	172-173 2-propanol	$C_{26}H_{19}N_3O_2$	75.57	5.02	11.02	75.45	4.91	10.98
8i	CH_3	H	3,4-$(CH_2O_2)C_6H_3$	C_6H_5	75	184-185 2-propanol	$C_{25}H_{19}N_3O_4$	70.58	4.50	9.88	70.69	4.67	9.76
9a	H	CH_3	CH_3CH_2	CH_3	20	191-193 ethanol	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	66.44	6.22	15.47
9b	H	CH_3CH_2	CH_3CH_2	CH_3	40	197-199 ethanol	$C_{16}H_{19}N_3O_2$	67.35	6.71	14.73	67.50	6.51	14.55
9c	H	H	C_6H_5	CH_3	50	240-243 ethanol	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76	70.79	4.60	13.92
9d	H	H	(*p*)$CH_3C_6H_4$	CH_3	60	230 dec. 2-propanol	$C_{19}H_{17}N_3O_2$	71.46	5.37	13.16	71.50	5.47	12.97
9e	H	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	40	175-176 ethanol	$C_{19}H_{15}N_3O_4$	65.32	4.33	12.03	65.63	4.46	12.32
9f	H	H	$CH_3(CH_2)_5CH_2$	CH_3	30	105-106 ethanol	$C_{21}H_{29}N_3O_2$	70.96	8.22	11.82	70.81	8.07	11.53

(a) Satisfactory ir and ^{1}H-nmr spectra were obtained for all the compound **8** and **9**. Uv spectra were recorded for the compounds **8h** and **8i** and ^{13}C nmr spectra for the compounds **8h** and **8i**.
(b) Compounds not recrystallized.

Scheme 5



10 **12**

11 **13**

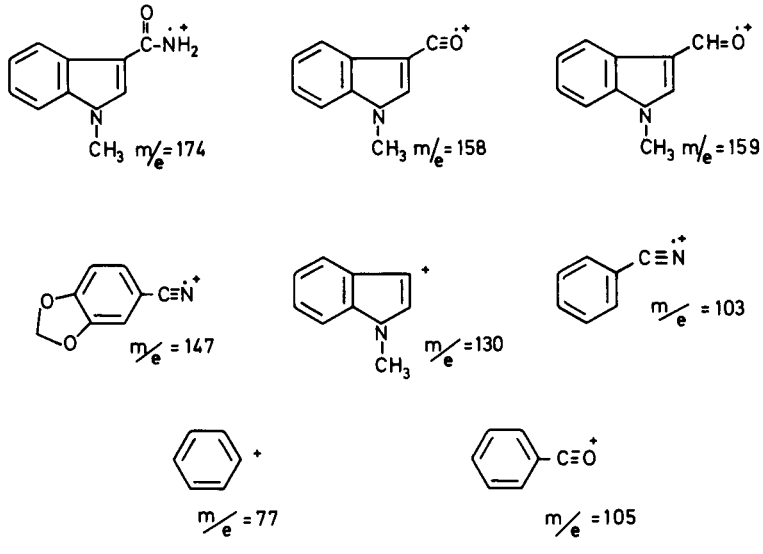
14

N^2-C=O and N^5-C=O, respectively. When the pyrrole nitrogen atom (N^5-H) is not substituted (compounds **6g-6n**), the ir spectra show a strong and broad band at about 3100-3400 cm^{-1} for the groups N^5-H and CONH. In all other cases, with no substituent on N^5, a feeble band for the CONH group is observed.

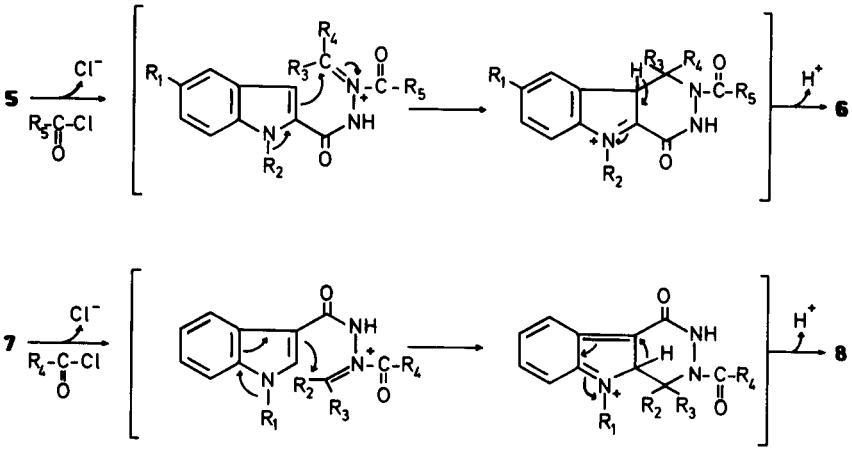
The most significant features of the ^{1}H-nmr spectra of compounds **6** are the following: the presence of a signal at about δ 8.00-8.50 (s, 1H) for the CONH group and the other one at about δ 6.80-7.10 (s, 1H), except in compounds **6b** and **6q**, which has been assigned to the proton C^1-H. This signal is very clean in the spectra of compounds **6a, 6d, 6e, 6g, 6i, 6j, 6k, 6l, 6m** and **6p**, while in the remaining cases it is masked by the signals corresponding to the aromatic protons. The value of δ for that assignment would seem very high, and in fact it is. However, in previous papers (1,2) we have reported values of δ 6.00-7.15 (DMSO-d_6) for the C^1-H group in some derivatives of 5*H*-pyridazino[4,5-*b*]indole, and Kogan and Vlasova (11) have reported δ 6.00 for compound **4** (R_1 = R_2 = R_3 = H, R_4 = C_6H_5) and δ 6.36 (trifluoroacetic acid) for compound **6** (R_1 = R_3 = H, R_2 = CH_3, R_4 = *p*-CH_3-C_6H_4). We cannot offer a satisfactory explanation for such high δ values for the proton of the C^1-H group.

The above considerations allow us to reject other possible structures for the compound **6**, consistent with the elemental analysis, as those represented by the formulas **10-14** (Scheme 5). The structures **10, 12** and **14** cannot support the signal assigned to the CONH group. Likewise, the structures **12** and **13** cannot support the observed carbonyl signals and they would show a signal about 1770-1800 cm^{-1}, characteristic for an enolic ester (22). On the other hand, a structure of a 1,3,4-oxadiazoline derivative, as represented by the formula **14**, is not compatible with the data from the ir and nmr spectra for compounds **6**. In the derivatives of 1,3,4-oxadiazoline, which could be obtained by treatment of hydrazones with acetic anhydride or by other means (14-21), the corresponding proton (R_3 = H) shows a signal at about δ 6.30 (14). Finally, the compounds with a structure as that represented by formula **11** would exhibit the signal of a mobile proton (NH) at about δ 5.0-5.4 (2) and not at about δ 8.0-8.5, as was observed in compounds **6**. All the preceding facts suggest that structure **6** is the correct one.

Scheme 6



Schema 7



In connection with the ^{1}H-nmr spectra of compounds **6** it has been observed that exchange of the proton of the CONH group with deuterium oxide in DMSO-d_6 is very slow and is stimulated by the addition of catalytic amounts of potassium hydroxide. This behaviour seems more expected for an NH group in an amide than in an amine. This fact also supports structure **6** and not structure **11**. On the other hand, it is interesting to note that in the presence of deuterium oxide, some of the signals in the ^{1}H-nmr spectra are resolved into two signals, as is detailed in the Experimental. This fact is probably a consequence of the partial double-bond character of the amide groups in structure **6**, with the stabilization of two rotational isomers, which is a well known behaviour of amides (22).

The structure of the derivatives of 1-oxo-5*H*-pyridazino-[4,5-*b*]indoles **8** and **9** were also confirmed through the study of their ir and ^{1}H-nmr spectra. The ir spectra show a broad band above 3000 cm^{-1} and frequently two bands, which were assigned to the groups NH and CONH, and two carbonyl bands about 1625-1660 and 1710-1720 cm^{-1}, assigned to the groups C^1=C and N^3 (R_4) C=O, respectively. The ^{1}H-nmr spectra show well characteristic signals at about δ 10.2-11.6 (sb, 1H) and 8.60-8.65 (sb, 1H) for the protons of the groups N^5-H and CONH, respectively. These last signals disappeared without other significant change in the spectra, by the addition of deuterium oxide. By the use of arguments similar to those discussed above for compounds **6**, structures derived from 3-indolyl of the type represented by the formulas **11-14** must be ruled out for compounds **9** (Table 2). On the other hand, consideration of the signals at about δ 7.00-8.50 and their integration suggest that the expected signal for the proton of the C^4-H group (formula **9**, R_2 = H) is mixed with a complex multiplet for the aromatic protons at about δ 7.9-8.5 for the compounds **9c**, **9d** and **9e**, with R_3 = aryl and about δ 7.2-7.8 for the compound **9f**, with R_3 = *n*-nonyl. However, these δ values for a proton with those characteristics are so high that we have had serious doubts about the structure of compounds **9**.

Consideration of the spectroscopic data for compounds **8** (Table 2) afforded similar results. The expected signal for the proton of the C^4-H group seem to be masked along with the signals for the aromatic protons into a complex multiplet at about δ 7.8-8.5 for the compounds **8c**, **8d** and **8e**, about δ 7.3-8.0 for the compound **6f**, and about 7.3-8.3 for the compounds **8g**, **8h** and **8i**. However, the spectra of the compounds **8c** and **8e** show a clean singlet at about δ 8.15-8.20 (1H). According to the above discussion, this signal must be assigned to the proton of the C^4-H group (formula **8**, R_2 = H).

In order to obtain some additional information about the structure of compounds **8**, we investigated the uv spectra of the hydrazones **7h** and **7i** and of their respective cyclization products **8h** and **8i**. The spectra of the hydrazones show essentially three bands with λ max 221, 282-283 and 317-330 nm. The spectra of the cyclization products also show essentially three bands at about λ max 211, 240-248 and 318-324 nm. On the other hand, there is an increase in the relative intensity for the bands of lower λ max and a decrease for the bands of higher λ max. However, these changes are not easily explained.

The mass spectra of the hydrazones **7h** and **7i** are relatively simple. Scheme 6 shows the tentative structure of the most important ions observed. Besides the corresponding molecular ions, both hydrazones show almost exclusively the same peaks below m/e 174, with a base peak of m/e 158. The peak of m/e 174 must proceed from a MacLafferty arrangement (22,23).

The mass spectra of the compounds **8h** and **8i** are more difficult to explain: both spectra show the peak corresponding to the molecular ions (15.5 and 10.0%, respectively) and a series of minor peaks between the molecular ion and m/e 159 which we could not interpret. Below m/e $\leq$ 159 both spectra show essentially the same peaks as the

spectra of the respective hydrazones with an additional new peak for m/e 105, corresponding to the benzoyl ion. The base peak has in both cases m/e 158, as in the spectra of the hydrazones. This similarity in the spectra of the hydrazones **7h** and **7i** and the corresponding products **8h** and **8i** suggests that the molecular ions from the last compounds are broken preferably to give the same ions which are produced by the hydrazones as molecular ions. This supposition could explain that, disregarding quantitative differences, the ions generated in all the spectra for m/e ≤ 159 are practically the same. For these reasons the mass spectra of the compounds **8** were not very useful to give us further structural information.

We have also studied the ^{13}C-nmr spectra of the compounds **7h** (R_1 = CH_3, R_2 = H, R_3 = C_6H_5), **7i** (R_1 = CH_3, R_2 = H, R_3 = 3,4-CH_2O_2-C_6H_3), **8h**, and **8i** in DMSO-d_6. The data obtained for the compounds **7h** and **7i** at room temperature are detailed with the experimental results and no further commentary is necessary. On the other hand, the spectra of compounds **8h** and **8i** above about 105 ppm were too complex and it was not possible to make unequivocal assignments of the signals. In addition, the spectra of compound **8h** at room temperature and at 60°, but not the spectra of compound **8i** at 60°, was further complicated because most of the carbon atoms of the compound generate double-signals in the spectra. This fact may be due to the presence of two rotational isomers because of the partial double-bond character of the C-N bond in amides (22), as was discussed above in connection with the ^{1}H-nmr spectra. Thus, a satisfactory interpretation of the spectra above of about 105 ppm was not possible.

However, the spectra show interesting signals below 105 ppm. The off-resonance decoupled spectra of compound **8h** at room temperature shows a double signal at about 33.3 and 33.0 ppm, with an intensity relation of 1.50, which unfolds into two quartets in the partial decoupled spectra. This signal was assigned to the CH_3 group, which shows a signal at about 33.0 (c) in the spectra of the respective hydrazone **7h**. On the other hand, a signal at about 92.5 ppm, which is resolved into a doublet in the partial decoupled spectra and is not present in the spectra of the respective hydrazone **7h**, was assigned to the C^4-H group of compound **8h**. On the contrary, the hydrazone **7h** shows a signal at about 143.8 (d) ppm for the CH=N group.

The spectrum of compound **8h** at room temperature and at 60° was similar to those of the preceding compounds without total collapsing of the double-signals as was expected. The only significant change observed below 105 ppm was a slight approximation of the double-signal assigned to the CH_3 group and a new intensity relation of about 1.70.

The ^{13}C-nmr spectra of compound **8i** was recorded only at 60°, with and without decoupling. The spectra show signals at about 33.3 (c), 101.4 (t) and 105.2 (d) ppm, which were assigned to the groups CH_3, CH_2O_2 and C^4-H, respectively. The spectra of the respective hydrazone **7i** show signals at about 32.9 (c), 101.2 (d) and 143.7 (d), assigned to the groups CH_3, CH_2O_2 and CH=N, respectively. The other signals for these spectra are detailed with the experimental results; their assignments are only tentative.

The above data discussed for compounds **8h** and **8i** suggest that the structure assigned to the compounds **8** is correct.

The Scheme 7 illustrates hypothetical and possible, but probable, mechanisms for the cyclization of the hydrazones **5** to the 4-oxo-5*H*-pyridazinoindole derivatives **6** and of the hydrazones **7** to the 1-oxopyridazinoindole derivatives **8** and **9**.

The compounds **6, 8** and **9** are labile to a long (3-4 hours) treatment with boiling ethanol or 2-propanol in the presence of acid (hydrochloric acid) or basic (potassium hydroxide, sodium ethoxide) catalysts. Under these conditions, compounds **6** gave the respective starting hydrazone **5** and compounds **8a-8f**. Also, compounds **9a-9f**, with an acetyl group on N^3, gave the respective hydrazone **7**; however, compounds **8g-8i**, with a benzoyl group on N^3, were degraded to the respective 1-benzoyl-2-(3-indolecarbonyl)hydrazine. Thus, starting with compounds **8h** or **8i** we obtained 1-benzoyl-2-(3-*N*-methylindolecarbonyl)-hydrazine. It is not difficult to formulate possible mechanisms for these degradations, similar but inverse to those which are illustrated in Scheme 7 for their formation from the starting hydrazones.

EXPERIMENTAL

Melting points were determined in capillary tubes on a warm plate and they are uncorrected. Elemental analysis were obtained on vacuum-dried samples (over phosphorus pentoxide at 3-5 mm, 2-3 hours at about 60-70°). Ir spectra were recorded on Perkin-Elmer 137E or 257 spectrometers, in potassium bromide tablets and the frequencies are expressed in cm^{-1}. ^{1}H-nmr spectra were obtained on Hitachi-Perkin-Elmer R-24A or R-12 (60 MHz) instruments or in a Varian Model XL-100 (100-MGc) spectrometer, using TMS as the internal reference, a concentration of about 0.1 g./ml. and the solvent indicated in each case. Uv spectra were recorded on a Unicam SP-1700 instrument. Mass spectra were obtained on a Perkin-Elmer Model RMU-6MG spectrometer by dirct injection. ^{13}C-nmr spectra were run on a Varian XL-100 apparatus.

Indolecarbohydrazones.

These compounds were obtained according to previously reported methods: 2-indolecarbohydrazones (24); 2-(5-benzyloxyindole)carbohydrazones (25); 2-(*N*-methylindole)carbohydrazones (26); 2-(*N*-methyl-5-benzyloxyindole)carbohydrazones (1); 3-indolecarbohydrazones (24) and 3-(*N*-methylindole)carbohydrazones (27). The following compounds were not previously reported and they were prepared by similar methods (1,24-27): 2-(5-benzyloxyindole)-*p*-chlorobenzylidenecarbohydrazone, m.p. 153-155°; 2-(*N*-methylindole)piperonylidenecarbohydrazone, m.p. 280° dec.; 2-(*N*-methyl-5-benzyloxyindole)piperonylidenecarbohydrazones, m.p. 245-246°; 3-indolepiperonylidenecarbohydrazone, m.p. 253-254°; 3-indolenonylidenecarbohydrazone, m.p. 216-218°.

The following spectroscopic data were not previously reported:

(a) 2-Indolecarbohydrazones (**5**).

This compound had ir (potassium bromide): 1620-1650 (s, C=O), 1600-1620 (s, m, C=N), 3040-3200 (s, m, COHN), 3150-3300 (m, N^1-H), 1385 cm^{-1} (m, N^1-CH_3); ^{1}H-nmr (DMSO-d_6): δ 6.70-7.90 (m, aromatic protons and -CH=N), 8.35-8.40 (s or Sb, 1H, CONH), 11.0-11.80 (Sb, 1H, NH indole), 4.00 (s, 3H, N^1-CH_3), 6.10 (s, 2H, 3,4-methylenedioxyaryl); 5.10 (s, 2H, $PhCH_2O$), 2.32-2.35 (s, 3H, p-CH_3Ar), 2.35 (s, 3H, CH_3-C(Ph)=).

(b) 3-Indolecarbohydrazones (**7**).

This compound had ir (potassium bromide): 1600-1630 (s, C=O), 1585-1615 (s, C=N), 3050-3200 (m, CONH), 3100-3400 cm^{-1} (m, N^1-H); ^{1}H-nmr (DMSO-d_6): δ 11.25-11.80 (Sb, 1H, N^1-H), 9.75-11.3 (Sb, 1H, CONH), 8.00-8.50 (m, 2H, H_2 + H_4), 7.00-7.90 (m, aromatic protons + H_{4-7} indole + CH=N), 6.10 (s, 2H, 3,4-methylenedioxyaryl), 2.30 (s, 3H, p-CH_3-Ar).

Compound **7** (R_1 = H, R_2 = CH_3, R_3 = C_2H_5).

This compound had nmr (DMSO-d_6): δ 1.95 (s, 3H, CH_3), 1.10 (t, 3H) and 2.35 (c, 2H) for C_2H_5.

Compound **7** (R_1 = H, R_2 = R_3 = C_2H_5).

This compound had nmr (DMSO-d_6): δ 1.05 (t, 3H) and 1.12 (t, 3H), $2CH_3$, 2.40 (m, 4H, $2CH_2$).

Compound **7** (R_1 = R_2 = H, R_3 = n-$(CH_2)_8CH_3$).

This compound had nmr (DMSO-d_6): δ 0.85 (t, 3H) 1.25 (m, 14 H), 2.25 (m, 2H).

Compound **7** (R_1 = H, R_2 = CH_3, R_3 = Ph).

This compound had nmr (DMSO-d_6): δ 2.35 (s, 3H, CH_3-C(Ph)=).

Compound **7h** (R_1 = CH_3, R_2 = H, R_3 = Ph).

This compound had uv (ethanol): λ max (log ε) 221 (4.54), 283 (4.30), 317 (4.46).

Compound **7i** (R_1 = CH_3, R_2 = H, R_3 = piperonyl).

This compound had uv (ethanol): λ max (log ε) 221 (4.58), 282 (4.22), 330 (4.48), 341 (sh, 4.38).

Compound **7h** (R_1 = CH_3, R_2 = H, R_3 = Ph).

This compound has ms: 277 (M^+, 5.2%), 174 (21.9), 159 (14.5), 158 (100), 130 (14.5), 103 (12.5), 77 (10.6).

Compound **7i** (R_1 = CH_3, R_2 = H, R_3 = piperonyl).

This compound had ms: 321 (M^+, 12.1%), 174 (37.9), 159 (16.3), 158 (100%), 147 (2.6), 130 (16.3), 103 (12.1).

Compound **7h** (R_1 = CH_3, R_2 = H, R_3 = Ph).

This compound had ^{13}C-nmr (DMSO-d_6): δ 143.8 (d, C_{10}), 143.7 (s, C_9), 134.4 (s, C_{7a}), 133.2 (d, C_2), 129.2 (d, C_4'), 128.5 (d, C_2'-, C_6'), 128.0 (s, C_1'), 126.5 (d, C_3'-C_5'), 122.0 (d, C_8), 121.2 (s, C_{3a}), 121.1 (d, C_4), 120.9 (s, C_3), 120.7 (d, C_6), 110.0 (d, C_7), 33.0 (c, C_8).

Compound **7i** (R_1 = CH_3, R_2 = H, R_3 = piperonyl).

This compound had ^{13}C-nmr (DMSO-d_6): δ 148.3 (s, C_9), 147.7 (s, C_4'), 143.7 (d, C_{10}), 136.7 (s, C_{7a}), 136.3 (s, C_3'), 133.0 (d, C_2), 128.9 (s, C_1'), 123.6 (d, C_6'), 122.5 (d, C_8), 122.0 (s, C_{3a}), 121.4 (s, C_3), 121.1 (d, C_4), 120.7 (d, C_6), 110.0 (d, C_7), 108.2 (d, C_5'), 104.8 (d, C_2'), 101.2 (t, C_{11}), 32.9 (c, C_8).

4-Oxo-1,2,3,4-tetrahydro (or 1-Oxo-1,2,3,4-tetrahydro)-5*H*-pyridazino-[4,5-*b*]indoles **6** and **8**.

Compound **6a-6m** and **8a-8f**.

To a stirred suspension of the corresponding 2- (or 3) indolecarbohydrazone (**5** or **7**, 3 mmoles, dried in vacuum over phosphorus pentoxide) in dried ethyl acetate (75 ml.) dried triethylamine (10 ml., 70 mmoles, freshly distilled) was added at room temperature. Acetyl chloride (5 ml., 70 mmoles, freshly distilled) in dried ethyl acetate (15 ml.) was slowly added to the suspension, maintaining the temperature below 40°. Stirring was continued until tlc (on Kieselgel HF 254-366, Merck, with benzene-dioxane-acetic acid, 90:25:4 v/v as solvent) showed that the reaction was complete (0.5-3 hours). The precipitate was filtered off, washed with ethyl acetate (2 × 10 ml.) and discarded. The combined filtrates were washed successively with water, 2*M* sodium bicarbonate and water, and the organic solution dried sodium sulfate. The solvent was removed in vacuum and the residue was digested with 2-propanol, collected by filtration and recrystallized (Tables 1 and 2).

The compounds **8a-8f** could not be satisfactorily recrystallized and they were transformed in the compounds **9a-9f** as indicated below.

Compounds **6n-6r** and **8g-8i**.

The reactions were carried out as was indicated above, but using benzoyl chloride (40 mmoles) instead of acetyl chloride. Chloroform was used as the solvent. The chloroform solution of the crude product was successively washed with water, 1 *N* hydrochloric acid and water, and then dried (sodium sulfate). The solvent was removed in vacuum and the crude product recrystallized (Tables 1 and 2).

Compounds **6a-6r** had ir (potassium bromide): cm^{-1} 1610-1690 (s, C^4=O); 1665-1730 (s, N^2-C=O); 1690-1705 (s, N^5-C=O); 1385-1400 (m, N^5-CH_3); 3100-3450 (s,m,w, CONH + N^5-H). The compounds with no substituent on N^5 (N^5-H) show a strong and broad band at about 3100-3450, but the compounds with a substituent on N^5 show a feeble band for CONH. Compounds **6a-6f, 6i, 6j, 6m** and **6o** (acetone-d_6) and compounds **6b, 6g, 6h, 6k, 6l, 6m, 6p-6r** (DMSO-d_6): had ^{1}H-nmr: δ = 11.80 (Sb, 1H, N^5-H, disappears by the addition of deuterium oxide); 8.00-8.65 (s, 1H, CONH, disappears by the addition of deuterium oxide and traces of potassium bromide); 6.70-8.40 (m, H_{6-9} and other aromatic protons); 6.80-7.10 (s, 1H, C^1-H); 2.70-2.75 (s, 3H, N^5-$COCH_3$); 2.50 (s, 3H, N^2-$COCH_3$); 3.90-4.10 (s, 3H, N^5-CH_3); 2.30 (s, 3H, C^1-CH_3); 6.00-6.10 (s, 2H, 3,4-CH_2O_2-aryl); 2.30-2.35 (s, 3H, p-CH_3-aryl); 2.25 (s, 3H, p-CH_3-COO aryl); 5.10 (s, 2H, aryl-CH_2O).

The proton of the group CONH exchanges very slowly with deuterium oxide and the corresponding signal on the spectra disappears by the addition of traces of potassium hydroxide (compounds **6b, 6k, 6l, 6m** and **6p**) and then most of the signals on the spectra were resolved into two signals; for example, with compound **6k** we observed: a) in DMSO-d_6: δ = 8.15 (s, 1H, CONH); 5.15 (s, 2H, $PhCH_2O$); 4.10 (s, 3H, N^5-CH_3); (b) in DMSO-d_6 + deuterium oxide: δ = 8.15 (s) and 8.55 (s) for CONH; 5.15 (s) and 5.20 (s), $PhCH_2O$; 4.10 (s) and 4.03 (s), N^5-CH_3; c) In DMSO-d_6 + deuterium oxide + potassium hydroxide: the same as in the case b), but the signals for CONH disappeared.

Compounds **8a-8i** had ir (potassium bromide): cm^{-1} 3100-3400 (w, CONH); 1625-1680 (s, C=O); 1680-1740 (s, $N^3(R_4)$C=O); 1645-1690 (s, N^5-C=O); 750-755 (s, 1,2-arom. disubst); ^{1}H-nmr (DMSO-d_6): δ = 8.40-8.60 (s, 1H, CONH) and the signal disappeared by the addition of deuterium oxide; 2.50-2.55 (s, 3H, N^5-$COCH_3$); 2.70-2.75 (s, 3H, N^3-$COCH_3$).

Compounds **8a-8f** had nmr (DMSO-d_6): δ 6.80-8.00 (m), 2H with **8a** and **8b**, 7H with **8c**, 6H with **8d**, 5H with **8e** and 3H with **8f**; 7.80-8.50 (m), 2H with **8a, 8b** and **8f**, 3H with **8c, 8d** and **8e**. Compounds **8g, 8h** and **8i** had nmr (DMSO-d_6): δ 7.30-8.30 (m), 18H with **8g**, 15H with **8h** and 13H with **8i**. Compound **8a** had nmr (DMSO-d_6): δ 1.60 (s, 3H, R_2 = CH_3), 0.90 (t, 3H) and 1.80 (c, 2H) for R_2 = C_2H_5. Compound **8b** had nmr (DMSO-d_6): δ 0.85 (t, 3H), 0.90 (t, 3H) and 2.30-2.50 (m, 4H) R_2 = R_3 = C_2H_5. Compounds **8d** and **8g** had nmr (DMSO-d_6): δ 2.30-2.35 (s, 3H, p-CH_3-Ph). Compounds **8e** and **8i** had nmr (DMSO-d_6): δ 6.05-6.10 (s, 2H, 3,4-CH_2O-aryl). Compound **8f** had nmr (DMSO-d_6): δ 0.85 (t, 3H, CH_3), 1.25 (Sb, 16H, -$(CH_2)_8$-). Compounds **8h** and **8i** had nmr (DMSO-d_6): δ 3.90-3.98 (s, 3H, N^5-CH_3).

Compound **8h** (R_1 = CH_3, R_2 = H, R_3 = R_4 = C_6H_5) had uv (ethanol): λ max (log ε) 211 (4.62), 248 (4.35), 290 (4.33), 318 (4.30). Compound **8i** (R_1 = CH_3, R_2 = H, R_3 = piperonyl, R_4 = C_6H_5) had uv (ethanol): λ max (log ε) 211 (4.65), 240 (sh, 4.38), 324 (4.24).

Compound **8h** had ms: m/e 381 (M^+, 15.5%), 364 (6.5), 319 (1.0), 288 (12.0), 285 (9.0), 220 (8.0), 218 (7.0), 175 (16.5), 159 (0.5), 158 (100), 130

(33.5), 105 (58.0), 103 (25.8), 77 (48.5). Compound **8i** had ms: m/e 425 (M^+, 10.0%), 407 (0.5), 278 (3.2), 159 (11.4), 158 (100), 130 (9.4), 105 (5.2), 103 (4.5). Compound **8h** had ^{13}C-nmr (DMSO-d_6 60°): δ = 92.5 (d, C^4-H); 33.3 (c) and 33.0 (c), CH_3. Above 105 ppm the spectra is too complex because most of the expected signals are present as double-signals. Compound **8i** had ^{13}C-nmr (DMSO-d_6 60°): δ = 170.0 (s, C_{11}); 166.4 (s, C_9); 149.3 (s, C_3'); 149.1 (d, C_6'); 147.7 (s, C_4'); 139.7 (d, C_4''); 137.3 (s, C_{7a}); 134.6 (s, C_2); 131.2 (d, C_3); 128.9 (d, $C_2''+C_6''$); 128.1 (s, C_{3a}); 127.7 (d, $C_3''+C_5''$); 126.2 (s, C_1''); 123.8 (d, C_5'), 123.2 (d, C_2'); 122.5 (s, C_1'); 120.6 (d, C_4); 110.9 (d, C_6); 109.5 (s, C_3); 108.2 (d, C_7); 105.2 (d, C_{10}); 101.4 (t, C_7'); 33.3 (c, C_8).

3-Acetyl-1-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indoles **9**.

A solution of the corresponding diacetyl derivative **8a-8f** (10 mmoles) in absolute ethanol (75 ml.) with a drop of 1*N* hydrochloric acid was refluxed for 0.5 hour. The solvent was removed and the crude product recrystallized (Table 2).

Compounds **9a-9f** had ir (potassium bromide): cm^{-1} 3020-3200 (m, NH indole + CONH, generally two bands); 1625-1660 (s, C^1=O); 1710-1720 (s, N^5-CO-R$_4$); 750-770 (s, 1,2-arom. disubst); ^{1}H-nmr (DMSO-d_6): δ = 10.2-11.6 (sb, 1H, N^5-H) and 8.60-8.65 (sb, 1H, CONH), these signals disappeared by the addition of deuterium oxide; 7.00-7.80 (m), 2H with the compounds **9a** and **9b**, 7H with **9c**, 6H with **9d**, 5H with **9e** and 3H with **9f**; 7.90-8.50 (m), 2H with the compounds **9a, 9b** and **9f**, 3H with **9c, 9d** and **9e**; 2.70-2.75 (s, 3H, N^3-COCH$_3$). Compound **9a** has ^{1}H-nmr (DMSO-d_6): 2.00 (s, 3H, R_2 = CH_3), 2.30 (c, 2H) and 1.15 (t, 3H, R_3 = C_2H_5). Compound **9b** had ^{1}H-nmr (DMSO-d_6): 1.05 (t, 3H, CH_3), 1.15 (t, 3H, CH_3), 2.00-2.40 (m, 4H, $2CH_2$). Compound **9d** had ^{1}H-nmr (DMSO-d_6): 2.35 (s, 3H, *p*-CH_3Ph). Compound **9e** had ^{1}H-nmr (DMSO-d_6): 6.10 (s, 2H, 3,4-CH_2O_2-aryl). Compound **9f** had ^{1}H-nmr (DMSO-d_6): 0.85 (t, 3H, CH_3), 1.30 (Sb, 16H,- $(CH_2)_8$-).

1-Benzoyl-2-(3-*N*-methylindolecarbonyl)hydrazine.

To a refluxing solution of 3-(*N*-methylindole)carbohydrazide (0.57 g., 3 mmoles) in chloroform (75 ml.), benzoyl chloride (0.5 g., 3 mmoles) was slowly added. The solution afterward boiled for 2 hours. Solvent was removed and the crude product recrystallized, m.p. 290-291° (ethanol-DMF); ir (potassium bromide): cm^{-1} 3030 (m) and 3220 (s), NH; 1655 (m) and 1630 (s), C=O; 695 (s) and 745 (s), arom. monosubst.; ^{1}H-nmr (DMSO-d_6): δ = 10.4 (Sb, 1H, CONH); 10.0 (Sb, 1H, CONH); 8.17 (s, 1H$_2$ indole); 7.80-8.50 (m, 3H, H_4 indole + H_2' and H_6' benzoyl); 3.82 (s, 3H, CH_3).

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