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Preparation of Carbamoyl Derivatives of Indole and of Derivatives of 1,2,4-Triazol-3-one from Semicarbazides

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A simple and one-step method for the preparation of the title compounds is described. Semicarbazides **2** react easily with levulinic acid in the presence of HCl to give **4**, whereas in an alkaline medium they cyclize to form the triazole derivatives **3**.

Darstellung der Carbamoylderivate des Indols und von Derivaten des 1,2,4-Triazol-3-ons aus Semicarbaziden

Ein einfaches und einstufiges Arbeitsverfahren zur Darstellung der Titelderivate wird beschrieben. Die aus den Formylderivaten **1** und Isocyanaten erhaltenen Semicarbazide **2** geben bei der Reaktion mit Lävulinsäure die Indol-Derivate **4**. Im alkalischen Medium zyklisieren die Semicarbazide zu den Triazol-Derivaten **3**.

Carbamoyl derivatives of indole, showing interesting pharmacological properties, were prepared so far by reaction of indole derivatives (containing no substituent at the nitrogen atom) with isocyanates[1]. However, due to the low reactivity of hydrogen in position 1, the hydrogen atom must be substituted by a metal (by treatment with sodium hydride or amide).

When derivatives of indolyl-3-acetic acid are used as starting materials for the preparation of derivatives of the general formula **4**, the reaction presents some difficulties; they result from the necessity of blocking the carboxyl group (esterification) and consequently, after reaction with isocyanates a saponification of the ester is necessary so as to obtain the appropriate derivatives of the acid. The saponification is a rather difficult procedure as the bond between carbamoyl substituent and nitrogen of the indole ring is unstable; in consequence, the saponification may cause a detachment of the substituent. Thus, the procedure used until now for the preparation of the carbamoyl derivatives **4** of indole is a rather complicated multistage process.

Taking into consideration the difficulties, we have undertaken the task to utilize 1-p-methoxyphenyl-2-formylhydrazine **1** for the preparation of the derivatives **4**; **1** is an intermediate in the manufacturing process of indometacin in industry[2] (see scheme). The question was whether a similar synthesis scheme might be used for the introduction of a

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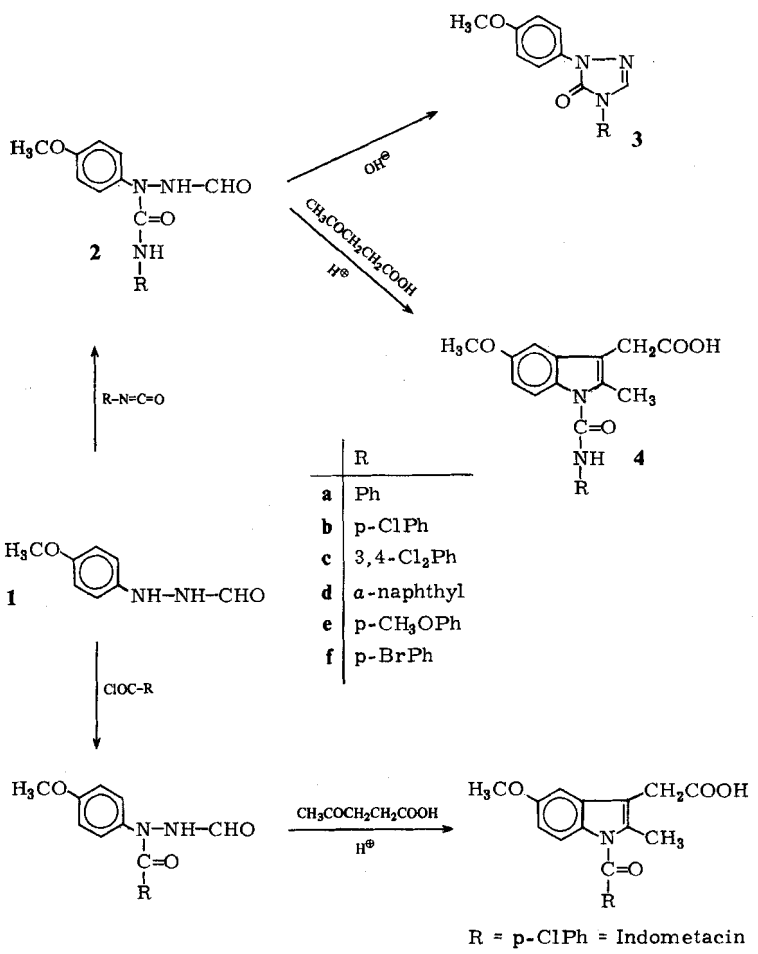

carbamoyl instead of an aroyl substituent so as to obtain derivatives of semicarbazide of the general formula **2**. Thus, compound **1** was brought to react with various isocyanates resulting in some new derivatives **2** in good yields (Table 1).

Semicarbazides of the general formula **2** may be considered to be derivatives of N^1-phenylcarbamoyl-N^2-formylphenylhydrazine. Hence, taking into account an analogy with the preparation process of indometacin[2], it could be expected that the derivatives **2** might react with ketones or aldehydes according to *Fischer*'s indolization reaction to give derivatives of indole **4**. The results of our work confirmed this supposition. It was found that derivatives **2** react easily with levulic acid in the presence of HCl forming some new indole derivatives of the general formula **4**.

The reaction of derivatives **2** with levulic acid is new because semicarbazide derivatives were hitherto not used as starting materials in the synthesis of indole compounds by *Fischer*'s method. On the other hand, the preparation method of carbamoyl derivatives **4**

by indolization of the appropriate derivatives of semicarbazide **2** is much more simpler than that used so far and makes it possible to obtain compounds **4** in a one step operation. Moreover, the method needs no hydrolysis of the formyl group although the group is not built into the ring system.

It is a well known fact that semicarbazides cyclize easily in an alkaline medium to form triazoles[3]. Thus, it seemed to be purposeful to utilize the intermediate products **2** for the preparation of some new derivatives **3** of 1,2,4-triazol-3-one (see scheme).

Table 1: *Compounds prepared*

Compd. No.	M.p. °C	Yield %	Formula (Mol. wt.)	C	H	N	calcd. found Cl	Br
2b	165–168	93	$C_{15}H_{14}N_3O_3Cl$ (319.7)	56.3 56.1	4.41 4.30	13.1 13.2	11.1 11.3	– –
2c	174–177	84	$C_{15}H_{13}N_3O_3Cl_2$ (354.2)	50.9 50.7	3.69 3.90	11.9 12.0	20.0 20.2	– –
2d	119–122	87	$C_{19}H_{17}N_3O_3$ (335.4)	68.0 68.2	5.11 5.32	12.5 12.6	– –	– –
2e	159–161	89	$C_{16}H_{17}N_3O_4$ (315.3)	60.9 61.0	5.43 5.57	13.3 13.5	– –	– –
2f	156–158	93	$C_{15}H_{14}N_3O_3Br$ (364.2)	49.5 49.3	3.87 3.62	11.5 11.6	– –	21.9 22.1
3b	202–204	70	$C_{15}H_{12}N_3O_2Cl$ (301.7)	59.7 59.5	4.01 4.00	13.9 13.8	11.7 11.8	– –
3c	176–178	72	$C_{15}H_{11}N_3O_2Cl_2$ (336.2)	53.6 53.9	3.29 3.32	12.5 12.7	21.1 21.4	– –
3d	143–147	61	$C_{19}H_{15}N_3O_2$ (317.3)	71.9 72.1	4.76 4.93	13.2 13.4	– –	– –
3e	159–161	90	$C_{16}H_{15}N_3O_3$ (297.3)	64.6 64.4	5.08 5.01	14.1 14.2	– –	– –
4b	206–208	38	$C_{19}H_{17}N_2O_4Cl$ (372.8)	61.2 61.0	4.59 4.82	7.5 7.7	9.5 9.8	– –
4c	213–215	54	$C_{19}H_{16}N_2O_4Cl_2$ (407.2)	56.0 56.3	3.96 4.04	6.9 6.7	17.4 17.1	– –
4e	182–184	69	$C_{20}H_{20}N_2O_5$ (388.4)	65.2 65.0	5.47 5.54	7.6 7.7	– –	– –
4f	200–202	40	$C_{19}H_{17}N_2O_4Br$ (417.3)	54.7 54.5	4.10 4.25	6.7 6.8	– –	19.1 19.2

Cl and Br were determinated by the *Schöniger* method

It is noticable that the formyl group plays a different role in the reactions described depending on the type of the synthesis. Hence, in the synthesis of semicarbazides from hydrazine derivatives it protects (blocks) one of the nitrogen atoms, in the synthesis of triazole derivatives it is a reacting group and is built into the ring system, whereas in the *Fischer*'s indolization process it does not take part in the reaction.

Experimental

Melting points: apparatus Tottoli (uncorr); *NMR spectra*: Jeol (Japan) JNM-C-60HL spectrometer; *elemental analysis*: automatic analyzer, model 1102, Carlo Erba (Italy).

1-Formyl-2-methoxyphenyl-4-phenylsemicarbazide **(2a)**

16.6 g (0.1 mole) of 1-(p-methoxyphenyl)-2-formylhydrazine was dissolved in 150 ml of $CHCl_3$, 130 ml of phenylisocyanate was added and the whole was heated under stirring at 50–55 °C for 2h. After cooling to 20° the precipitate was washed with 2 × 50 ml of $CHCl_3$ and dried to give 26 g of **2a**, m.p. 162–164 °C, yield 91.5 %. $C_{15}H_{15}N_3O_3$ Calcd.: C 63.2 H 5.30 N 14.7; Found: C 63.1 H 5.39 N 14.6; NMR (15 % solution in CD_3SOCD_3, TMS) δ (ppm) = 3.76 (s, 3H), 6.90–7.80 (m, 9H), 8.21 (s, 1H), 8.88 (s, 1H), and 10.68 (s, 1H).

2-(p-Methoxyphenyl)-4-phenyl-1,2,4-triazol-3-one **(3a)**

5 g of NaOH was dissolved in 350 ml of methanol, 28.5 g **2a** was added, and the whole was stirred at room temp. for 4 h and then, at 45 °C for 2 h. After cooling the precipitate was washed with methanol, and dried to give 12.5 g of **3a** m.p. 178–179 °C, yield 94 %. $C_{15}H_{13}N_3O_2$ Calcd.: C 67.4 H 4.87 N 15.7; Found: C 67.6 H 4.96 N 15.6; NMR (10 % solution in CD_3SOCD_3, TMS) δ (ppm) = 3.81 (s, 3H) 7.00–7.94 (m, 9H), 8.70 (s, 1H).

1-(Phenylcarbamoyl)-2-methyl-5-methoxyindolyl-3-acetic acid **(4a)**

60 ml of glacial acetic acid was saturated with 4–5 g of gaseous HCl, 60 g of levulic acid and 20 g of **2a** were added, and the whole was stirred at room temp. for 3 h and left to stand overnight. The precipitated product was washed with glacial acetic acid, macerated with 200 ml of benzene at 50–60 °C, washed with 50 ml of benzene, and dried. The crude product was recrystallized from a mixture of acetone and water. Average yield was 32.5 g (46 %) of **4a** m.p. 183–185 °C. $C_{19}H_{18}N_2O_4$ Calcd: C 67.4 H 5.36 N 8.3; Found: C 67.7 H 5.26 N 8.3; NMR (15 % solution in CD_3SOCD_3, TMS) δ (ppm) = 2.51 (s + DMSO), 3.72 (s, 2H), 3.83 (s, 3H), 6.78–7.90 (m, 9H), 10.54 (s, 1H).
Other compounds, listed in Table 1, were prepared similarly.

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