Chem. Pharm. Bull.
32(8)3252—3254(1984)

A New Ring Transformation of 3,4-Dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-ones into 1-(Methylcarbamoyl)-methyl-3-phenyl-1*H*-indazoles

YASUO FUJIMURA,* HIROYUKI NAGANO, ISAO MATSUNAGA, and MINORU SHINDO

Central Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada 3–41–8, Toshima-ku, Tokyo 171, Japan

(Received November 29, 1983)

3,4-Dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one (**1a**) readily undergoes a transformation into 1-(methylcarbamoyl)methyl-3-phenyl-1*H*-indazole (**3a**) when its chloroform solution is kept at room temperature. The 8-chloro, 8-bromo and 8-fluoro derivatives of **1a** (**1b**, **1c** and **1d**) similarly afford the corresponding 5-halogenoindazoles (**3b**, **3c** and **3d**), but 3,4-dihydro-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one, and its 1-benzyl and 1-dialkylaminoalkyl derivatives give no ring contraction product under the same conditions.

Keywords——3,4-dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one derivative; ring contraction; spiro type intermediate; 1-(methylcarbamoyl)methyl-3-phenyl-1*H*-indazole derivative

We previously reported on the synthesis and biological activities of various 3,4-dihydro-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one derivatives.[1] In the course of these studies, we happened to find a ready transformation of 3,4-dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-ones (**1**) into 1-(methylcarbamoyl)methyl-3-phenyl-1*H*-indazoles (**3**).

As described previously, 8-chloro-3,4-dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one (**1b**) can be purified by chromatography on silica gel with benzene–ether–chloroform (1 : 1 : 1, v/v), and the nuclear magnetic resonance (NMR) spectrum of **1b** in $CDCl_3$ is fully consistent with this structure. Nevertheless, it was observed that crystals began to precipitate from a solution of **1b** upon standing for several hours. Some preliminary examinations suggested that an isomerization of **1b** had occurred.

In exploring this isomerization in detail, a solution of 3,4-dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one (**1a**) in chloroform was allowed to stand at room temperature overnight. Although no crystals appeared in this case, thin-layer chromatography indicated that **1a** had been converted almost completely into a single product (**3a**). The analytical data and the mass spectrum (MS) (M^+, *m/z*: 265) indicated that **3a** has the same molecular formula as **1a**, $C_{16}H_{15}N_3O$. On the basis of the spectroscopic data described in the experimental section, **3a** was assigned the structure 1-(methylcarbamoyl)methyl-3-phenyl-1*H*-indazole.

In order to obtain an authentic sample of **3a**, 3-phenyl-1*H*-indazole (**4**)[2] was treated with ethyl bromoacetate to give the 1-ethoxycarbonylmethyl derivative (**5**), which was transformed into **3a** by treatment with aqueous methylamine solution. Thus, the structure of **3a** was unambiguously established.

It was further shown that the 8-chloro, 8-bromo and 8-fluoro derivatives of **1a** (**1b**, **1c** and **1d**) also undergo the same type of transformation under the same conditions, and the structures of **3b**, **3c** and **3d** were similarly established (Chart 1).

The ring transformation of **1** into **3** may be reasonably rationalized by the course through the spiro-type intermediate (**2**), as formulated in Chart 1.

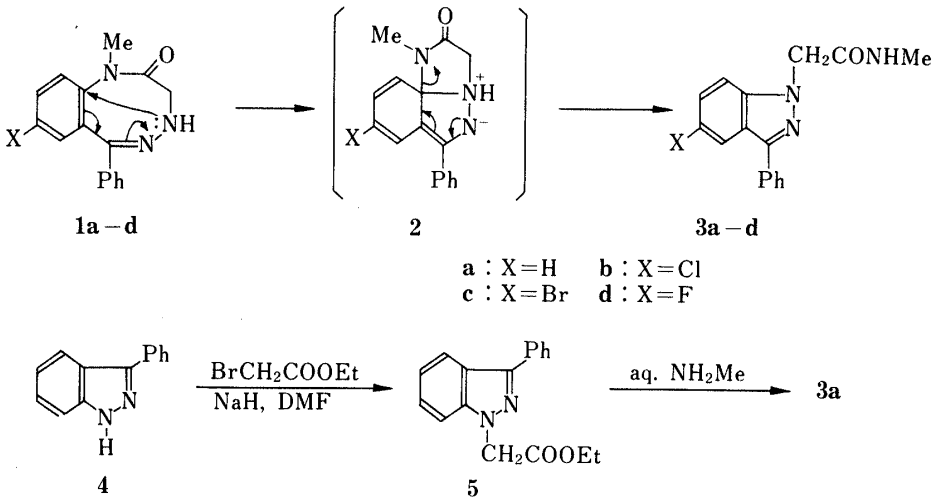

Chart 1

TABLE I. 1-(Methylcarbamoyl)methyl-3-phenyl-1*H*-indazoles (**3a—d**)

Compound No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3a	90	167—168	$C_{16}H_{15}N_3O$	72.43	5.70	15.84
				(72.57	5.70	15.86)
3b	92	200	$C_{16}H_{14}ClN_3O$	64.11	4.71	14.02
				(64.14	4.74	13.78)
3c	88	210	$C_{16}H_{14}BrN_3O$	55.83	4.10	12.21
				(55.73	4.12	12.01)
3d	84	173—175	$C_{16}H_{14}FN_3O$	67.83	4.92	14.83
				(67.98	4.99	14.79)

However, curiously, the ring contraction was not observed with 3,4-dihydro-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one and its 1-benzyl[3] and 1-dialkylaminoalkyl[4] derivatives under the above-mentioned conditions, though the possibility of the ring contraction of these compounds under stronger conditions has not yet been investigated.

Experimental

All melting points are uncorrected. NMR spectra were obtained on a Hitachi RB-24 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 instrument. Infrared (IR) spectra were measured on a Hitachi 260-30 infrared spectrophotometer.

Transformation of 4,5-Dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-ones (1) into 1-(Methylcarbamoyl)methyl-3-phenyl-1*H*-indazoles (3)——A solution of 4,5-dihydro-1-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)-one (**1a**, 1 g) in $CHCl_3$ (20 ml) was kept at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from acetone–*n*-hexane to give 1-(methylcarbamoyl)methyl-3-phenyl-1*H*-indazole (**3a**, 0.90 g), colorless crystallines, mp 167—168 °C. MS *m/z*: 265 (M^+), 207 ($M^+ - 58$). NMR ($CDCl_3$) δ: 2.70 (3H, d, J=8 Hz, –NH–C<u>H</u>$_3$), 5.03 (2H, s, –C<u>H</u>$_2$CO–), 5.90 (1H, m, N<u>H</u>), 7.3—8.1 (9H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3300, 1660.

The transformation of the 8-chloro, 8-bromo and 8-fluoro derivatives (**1b**, **1c** and **1d**) into the corresponding 5-halogenoindazoles (**3b**, **3c** and **3d**) was effected in a similar manner. The yields, melting points and elemental analytical data of **3a—d** are summarized in Table I.

Synthesis of 3a from 3-Phenyl-1*H*-indazole (4)——A solution of **4** (1.94 g) in dimethylformamide (DMF) (30 ml)

treated with NaH (*ca.* 50% in mineral oil, 0.58 g). The mixture was stirred at room temperature for 10 min, then ethyl bromoacetate (2.0 g) was added, and the whole was stirred for 30 min, poured into ice-water and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 1-ethoxycarbonylmethyl-3-phenyl-1*H*-indazole (**5**, 2.0 g) as an oil. NMR ($CDCl_3$) δ: 1.00 (3H, t, $-OCH_2C\underline{H}_3$), 3.98 (2H, q, $-OC\underline{H}_2CH_3$), 4.94 (2H, s, $-C\underline{H}_2CO-$), 7.00—8.00 (9H, m, aromatic H).

A solution of **5** (1.0 g) in EtOH (10 ml) was treated with 25% aq. NH_2CH_3 (0.91 g). The mixture was kept at room temperature overnight, then concentrated under reduced pressure and extracted with $CHCl_3$. The extract was washed with water, dreid over Na_2SO_4, and concentrated, and the residue was recrystallized from acetone–*n*-hexane to give **3a** (0.6 g), mp 167—168 °C, undepressed on admixture with a specimen of **3a** obtained from **1a**.

References

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