A FACILE STEREOSELECTIVE SYNTHESIS OF NOVEL HETEROCYCLES WITH HEXAHYDRO-2H-INDAZOLE, THIAZOLE, AND COUMARIN MOIETIES

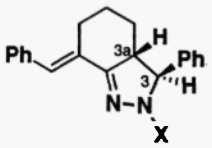
Yaroslav V. Bilokin (Belokon),*[a1] and Ivan M. Gella[b]

[a] *Department of Organic Chemistry, Ukrainian Academy of Pharmacy, 310002 Kharkov, Ukraine*
[b] *Department of Organic Chemistry, Kharkov State University, 4 Svobody sq., 310077 Kharkov, Ukraine*

Abstract: A series of novel 3-(2-(7-benzylidene-3-phenyl-3,3a-*cis*-3,3a,4,5,6,7-hexahydro-2H-indazol-2-yl)thiazol-4-yl)-2H-1-benzopyran-2-one derivatives **7a-i** have been synthesized stereoselectively by condensation of 3-(ω-bromoacetyl)-coumarins **6a-d** with 3,3a-*cis*-7-benzylidene-3-phenyl-2-thiocarbamoyl-3,3a,4,5,6,7-hexahydro-2H-indazoles **4a-d**.

Dihydropyrazoles of type **1** and **2** have a wide range of biological activities (2), namely, they are central nervous system depressants, anti-inflammatory agents, fungicides, and bactericides. This type of compounds can be formed as 3,3a-*cis*- or *trans*-isomers or as a mixture in the reaction media but it is known (3) that the stereochemistry of biologically active compounds performs a significant role as far as drug-receptor interactions are influenced.

In the continuation of our studies (4) on the chemistry of dihydropyrazole derivatives, in this communication we wish to report on a facile stereoselective synthesis of novel 3,3a-*cis*-hexahydro-2H-indazole derivatives substituted at 2-position with heterocyclic fragments such as thiazole and coumarin.



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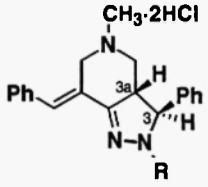

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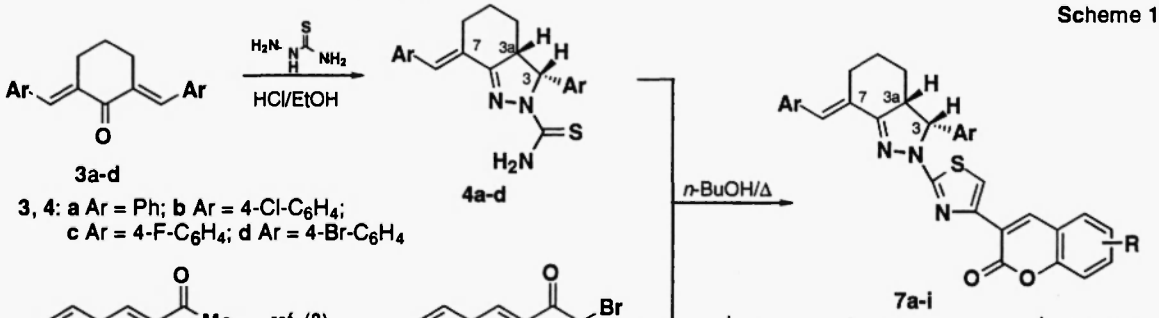
N-Thiocarbamoylhexahydroindazoles **4a-d** were synthesized (4,5) by the reaction of α,α'-bis(substitutedbenzylidene)cyclohehanones **3a-d** (6) with thiosemicarbazide in ethanol, catalyzed by hydrochloric acid. It is noteworthy that in the reactions only one 3,3a-*cis*-isomer was obtained in each case. The Hantzsch method is one of the common pathway for thiazole synthesis (7) and it entitles the preparation of a large variety of differently substituted thiazoles by starting from *N*-unsubstituted thioamides and α-halogeno carbonyl compounds.

3-(ω-Bromoacetyl)coumarins **6a-d** (8) obtained by bromination of 3-acetylcoumarins **5a-d** (9) were condensed in boiling *n*-butanol with *N*-thiocarbamoylhexahydroindazoles **4a-d** to form (Scheme 1) the corresponding 3,3a-*cis*-hexahydro-2H-indazole derivatives **7a-i** (10) substituted at 2-position.

Scheme 1



3a-d

3, 4: **a** Ar = Ph; **b** Ar = 4-Cl-C_6H_4; **c** Ar = 4-F-C_6H_4; **d** Ar = 4-Br-C_6H_4

4a-d

5a-d

5, 6: **a** R = H; **b** R = 6-Br; **c** R = 5,6-benzo; **d** R = 6-*n*-C_6H_{13}, 7-OH

6a-d

7a-i

	Ar	R	Yield, %
6a + 4a → 7a	Ph	H	87
6a + 4b → 7b	4-Cl-C_6H_4	H	79
6a + 4c → 7c	4-F-C_6H_4	H	74
6a + 4d → 7d	4-Br-C_6H_4	H	73
6b + 4a → 7e	Ph	6-Br	77
6b + 4c → 7f	4-F-C_6H_4	6-Br	71
6c + 4a → 7g	Ph	5,6-benzo	91
6d + 4a → 7h	Ph	6-*n*-C_6H_{13}, 7-OH	75
6d + 4b → 7l	4-Cl-C_6H_4	6-*n*-C_6H_{13}, 7-OH	72

It should be pointed that under reaction conditions no isomerization of *exo*-cyclic double bond into cyciohexane ring was observed as it was reported (4) before. 3,3a-*Cis* configuration assignments for the compounds **4a-d** and **7a-i** were corroborated (4,10,11) on the ground of the spin coupling constants $J_H{}^3H^{3a}$ which were in the range 10.8...11.2 Hz and it corresponds to the fact that values of $J_H{}^3H^{3a}$ (*cis*) are greater than those of $J_H{}^3H^{3a}$ (*trans*) and are in the region reported (4,11), namely, 10...14 Hz for the *cis*- and 3...10 Hz for the *trans*-isomers. The IR spectra of the compounds **7a-i** exhibited the characteristic $C_{(5)}$-H thiazole stretching vibrations (12) with medium intensity in the region 3135-3145 cm^{-1}.

In summary, 3,3a-*cis*-hexahydro-2H-indazole derivatives **7a-i** substituted at 2-position with heterocyclic moieties such as thiazole and coumarin have been synthesized by condensation of 3-(ω-bromoacetyl)coumarins 6a-d with *N*-thiocarbamoylhexahydroindazoles **4a-d**.

References and Notes

(1) Present address: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

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(5) All chiral compounds in this work are racemic; only one enantiomer of each pair is addressed to in the text and displayed in the structural formulas. All new compounds showed spectroscopic and analytical data consistent with assigned structures.

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(10) The ^1H NMR spectra of the compounds **7a-i** exhibited the following relevant signals: (400 MHz, DMSO-d_6) δ 5.87...5.91 (d, $J_H{}^3H^{3a}$= 10.8...11.2 Hz, 3-$CH_{indazole}$); 7.70...7.74 (s, 5-$CH_{thiazole}$) and 8.21 (s, 4-$CH_{coumarin}$)

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