*Chemistry of Heterocyclic Compounds, Vol. 33, No. 12, 1997*

# 2-PYRAZOLINES ON THE BASIS OF DIARYLIDENE-CYCLOHEXANONES.

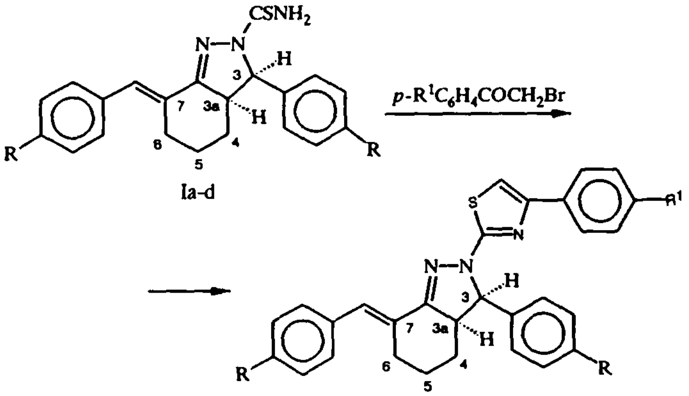
# SYNTHESIS AND STEREOCHEMISTRY OF N-THIO-CARBAMOYL AND N-THIAZOLYL DERIVATIVES

**I. M. Gella, Razak Yaya Amadu, G. V. Cherkaev,**
**S. V. Fialkova, and V. D. Orlov**

*In the interaction of N-thiocarbamoylhexahydroindazoles with α-bromoacetophenones, the corresponding N-thiazolylpyrazolines are formed. In some cases, the heterocyclization is accompanied by a shift of the double bond and cis-trans isomerization in the pyrazoline ring. A study has been made of the influence of the stereochemistry of these compounds on their spectral and luminescence properties.*

Reactions of diarylidencyclanones with hydrazine and alkylhydrazines produce the corresponding pyrazolines in the form of the 3,3a-trans isomers [1-3]. In the interaction of a benzylidenecyclanone or dibenzylidenecyclanone with semicarbazide in an acidic medium, the usual product is a mixture of cis and trans isomers, whereas in the reaction of dibenzylidenecyclohexanone with thiosemicarbazide, the sole product is usually that with the cis configuration of the hydrogen atoms on the pyrazoline ring [4].

We found that substituted diarylidenecyclohexanones react analogously with thiosemicarbazide, forming N-thiocarbamoylhexahydroindazoles (I). The similarity of the PMR spectra of compounds Ia-d (Table 1) indicates that, in all cases, the products that are formed have the same orientation of the substituents at $C_{(3)}$.



I-IV a) R = H; b) R = Cl; c) R = $NO_2$; d) R = $NMe_2$;
IIa-d) $R^1$ = H; IIIa-c) $R^1$ = Br; IVa,c) $R^1$ = Ph

Cyclization of the thioamides Ia-d with phenacyl halides affords the N-(2-thiazolyl)hexahydroindazoles II-IV. In the PMR spectra of these compounds (Table 1), the signal of the H-5 proton of the thiazole ring is observed in the form of a separate singlet (6.7-6.8), whereas the signal of the vinyl proton of the arylidene group close to 7.5 ppm is overlapped by signals of the aromatic protons. The signal of the H-3 proton of the pyrazoline ring is observed in the 5.7-6.2 ppm region in the form of a doublet with SSCC approximately 11 Hz. The signals of the cyclohexane protons are located in the 0.8-3.5 ppm

---

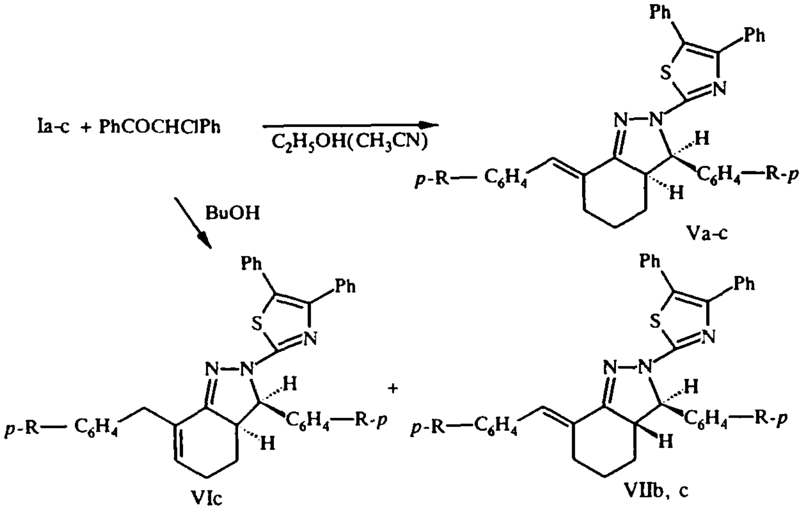
Khar'kov State University, Khar'kov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1650-1654, December, 1997. Original article submitted December 2, 1996; revision submitted April 1, 1997.

TABLE 1. PMR Spectra of Synthesized Compounds

| Compound | Chemical shifts of aliphatic protons δ, ppm | | | | | | | | SSCC |
|---|---|---|---|---|---|---|---|---|---|
| | $H_{(3)}$ | $H_{(3a)}$ | $H_{(6e)}$ | $H_{(6a)}$ | $H_{(5e)}$ | $H_{(4e)}$ | $H_{(5a)}$ | $H_{(4a)}$ | $^3J_{3,3a}$ |
| Ia | 5,97 | 3,58 | 2,84 | | | 1,65 | | 0,65 | |
| Ib | 6,03 | 3,48 | 2,94 | 2,19 | 1,84 | 1,72 | 1,44 | 0,81 | 10,8 |
| Ic | 6,16 | 3,59 | 2,96 | 2,25 | 1,89 | 1,77 | 1,48 | 0,79 | |
| IIa | 5,84 | 3,57 | 2,99 | 2,22 | 1,82 | 1,74 | 1,45 | 0,93 | 11,0 |
| IIb | 5,8 | 3,55 | 2,92 | 2,19 | 1,84 | 1,72 | 1,45 | 0,91 | 11,2 |
| IIc | 5,96 | 3,68 | 2,96 | 2,28 | 1,91 | 1,79 | 1,52 | 0,876 | 11,3 |
| IId | 5,72 | 3,50 | | 2,27 | 1,83 | 1,71 | 1,47 | 1,05 | 10,8 |
| IIIa | 5,8 | 3,58 | 3,00 | 2,22 | 1,82 | 1,72 | 1,46 | 0,936 | 10,9 |
| IIIb | 5,76 | 3,56 | 2,95 | 2,20 | 1,86 | 1,72 | 1,49 | 0,92 | 11,3 |
| IIIc | 5,95 | 3,69 | 2,97 | 2,28 | 1,91 | 1,75 | 1,55 | 0,87 | 11,0 |
| IVa | 5,91 | 3,59 | 3,00 | 2,23 | 1,8 | 1,8 | 1,46 | 0,91 | 11,9 |
| IVc | 5,98 | 3,7 | 2,98 | 2,3 | 1,8 | 1,8 | 1,5 | 0,89 | 11,4 |
| Va | 5,83 | 3,56 | 3,0 | 2,23 | 1,82 | 1,75 | 1,49 | 0,932 | 11,0 |
| Vb | 5,79 | 3,56 | 2,92 | 2,2 | 1,85 | 1,71 | 1,49 | 0,91 | 11,0 |
| Vc | 6,14 | 3,92 | 2,91 | 2,42 | 1,97 | 1,82 | 1,53 | 0,75 | 11,6 |
| VIc | 5,8 | 3,59 | 2,98 | 2,98 | 2,88 | 2,56 | 1,62 | 0,86 | 11,6 |
| VIIb | 4,95 | 3,1 | 3,0 | 3,0 | 2,18 | 1,89 | 1,5 | 1,68 | 11,5 |
| VIIc | 5,06 | 3,09 | 2,97 | 2,44 | 2,18 | 1,98 | 1,5 | 1,72 | 11,9 |
| VIIe | 5,12 | 3,2 | 3,02 | 2,53 | 2,26 | 2,03 | 1,55 | 1,78 | 11,9 |

region. It was noted in [4, 5] that the chemical shifts of protons at $C_{(3)}$ and $C_{(3a)}$ differ by more than 0.5 ppm for diastereomeric pairs of pyrazolines with pseudoequatorial and pseudoaxial phenyl group in position 3. Since the chemical shifts of the protons at $C_{(3)}$ and $C_{(3a)}$ are close together in the case of compounds I-IV, this means that they all have an identical configuration at $C_{(3)}$.

Through the interaction of the thioamides I with α-chlorodesoxybenzoin, the corresponding derivatives of 4,5-diphenylthiazole Va-c are formed. The low solubility of the nitro-substituted thioamide Ic in ethanol greatly retards the cyclization; therefore, we attempted to carry out this reaction in a higher-boiling solvent, namely butanol. Here, in the reaction of Ic with α-chlorodesoxybenzoin, we obtained a mixture of two isomeric compounds, VIc and VIIc, differing in PMR spectra from the expected cyclization product Vc. Subsequently, we succeeded in obtaining the isomer Vc by performing the cyclization in acetonitrile.



In the PMR spectrum of compound VIc, we observe additional signals in the form of a broadened singlet at 6.05 ppm, characteristic for the vinyl proton on the cyclohexane ring, and the spin system AB formed by the pair of benzyl protons at 3.77 ppm. Consequently, the formation of VIc is accompanied by migration of the exocyclic double bond into the cycloxane ring, under the influence of the HCl evolved in the course of the cyclization. This sort of double-bond migration into the ring in the presence of strong acids is known in the case of arylidenecyclohexanones [6]. The chemical shifts of the protons of the

TABLE 2. Characteristics and Spectral-Luminescence Properties of Synthesized Compounds

| Compound | Empirical formula | N found, % | N calculated, % | mp, °C | UV spectrum, $\lambda_{max}$ (and $\varepsilon \cdot 10^3$) | Fluorescence | | Yield, % |
|---|---|---|---|---|---|---|---|---|
| | | | | | | $\lambda_{exc}$, nm (and quantum yield) | Stokes shift, $cm^{-1}$ | |
| Ia* | $C_{21}H_{21}N_3S$ | | | 208...210 | | | | 59 |
| Ib | $C_{21}H_{19}Cl_2N_3S$ | 10,2 | 10,1 | 158...160 | | | | 55 |
| Ic | $C_{21}H_{19}N_5O_4S$ | 16,2 | 16,0 | 236...240 | | | | 60 |
| Id † | $C_{25}H_{31}N_5S$ | 16,0 | 16,2 | 175...180 | | | | 72 |
| IIa | $C_{29}H_{25}N_3S$ | 9,5 | 9,4 | 198...201 | 373 (12,4), 282 (23,5) | 540 (0,12) | 8280 | 54 |
| IIb | $C_{29}H_{23}Cl_2N_3S$ | 8,3 | 8,1 | 192...194 | 379 (26,4), 287 (34,82) | 551 (0,12) | 8440 | 42 |
| IIc | $C_{29}H_{23}N_5O_4S$ | 12,9 | 13,0 | 236...239 | 416 (24,02), 290 (34,42) | 618 (0,03) | 7840 | 34 |
| IIIa | $C_{29}H_{24}BrN_3S$ | 8,1 | 8,0 | 205...208 | 372 (26,9), 263 (38,0) | 538 (0,06) | 8300 | 60 |
| IIIb | $C_{29}H_{22}BrCl_2N_3S$ | 6,9 | 7,1 | 190...195 | 371 (26,98), 264 (37,8) | 550 (0,09) | 8800 | 44 |
| IIIc | $C_{29}H_{22}BrN_5O_4S$ | 11,2 | 11,4 | 195...198 | 393 sh, 283 sh, 262 (38,24) | | | 32 |
| IVa | $C_{35}H_{29}N_3S$ | 8,2 | 8,0 | 193...196 | 370 (27,06), 280 (35,74) | 545 (0,06) | 8720 | 52 |
| IVb | $C_{35}H_{27}Cl_2N_3S$ | 7,0 | 7,1 | 107...110 | 363 sh, 308 sh, 278 (35,84) | 540 (0,06) | | 55 |
| IVc | $C_{35}H_{27}N_5O_4S$ | 11,5 | 11,4 | 214...217 | 414 (24,18), 302 (33,14), 286 (36,26) | 623 (0,03) | 8120 | 75 |
| Va | $C_{35}H_{29}N_3S$ | 8,1 | 8,0 | 104...107 | 368 (12,70), 278 (20,72) | 569 (0,04) | 9540 | 45 |
| Vb | $C_{35}H_{27}Cl_2N_3S$ | 6,9 | 7,1 | 111...115 | 371 (26,98), 289 (34,56) | 579 (0,05) | 9800 | 58 |
| Vc | $C_{35}H_{27}N_5O_4S$ | 11,6 | 11,4 | 202...203 | | | | 46 |
| VIc | $C_{35}H_{27}N_5O_4S$ | 11,5 | 11,4 | 121...124 | 342 (29,24), 268 (37,26) | | | 38 |
| VIIc | $C_{35}H_{27}N_5O_4S$ | 11,4 | 11,4 | 226...229 | 268 (37,2) | | | 66 |
| VIII ‡ | $C_{23}H_{20}N_2$ | | | 179...180 | 388 (25,8) | 482 (0,9) | 5040 | |

---

*Literature mp 210°C [4].

†Mixture of cis-trans isomers.

‡Literature mp 176-177°C [7].

pyrazoline ring in compounds IIc and VIc are not significantly different from each other; this means that the double-bond migration does not affect the orientation of the substituents in the pyrazoline ring.

The spectrum of compound VIIc still contains signals of the pyrazoline-ring protons, but they have been shifted downfield by 0.6-0.8 ppm. It was shown in [5] in the example of 1,2-diphenylhexahydroindazole that such changes are related to cis-trans isomerism in the pyrazoline ring. Attention should also be directed to the differences in chemical shifts of the $H_{(4a)}$ protons of the diastereomeric compounds Vc and VIIc (Table 1). In the spectrum of the isomer Vc, its signal is shifted 0.97 ppm downfield as a consequence of shielding of the phenyl group at $C_{(3)}$. Shielding is possible only for the cis-3,3a isomer, in which the axial proton at $C_{(3)}$ can be located above the plane of the phenyl ring. Such cis-trans isomerization is not restricted to the case of the nitro derivative: When the time of interaction of Ib with α-chlorodesoxybenzoin was extended, the trans isomer VIIb appeared in the reaction mixture along with the Vb (in this case, double-bond migration was not observed).

We believe that, along with the noted differences in chemical shifts of the protons at $C_{(3)}$ and $C_{(3a)}$, the magnitude of the chemical shift of $H_{(4a)}$ can be used in determining the orientation of the substituent at $C_{(3)}$ (cis or trans orientation of the hydrogen atoms at $C_{(3)}$ and $C_{(3a)}$). The magnitude of the vicinal SSCC $J_{3,3a}$ cannot be used to draw any conclusion regarding the configuration of the pyrazoline-ring protons in the diastereomers that were obtained, since these values are very close together.

The absorption spectra of the compounds that we obtained contain two or three bands; the most intense are the short-wave bands at 260-290 nm (Table 2). Whereas the most intense absorption band in the spectrum of 1,3-diphenyl-3-styrylpyrazoline (VIII) is the long-wave band, 388 nm in dioxane, we find that in the spectra of the compounds that we obtained, despite the enlargement of the π-system, this band becomes less intense and is hypsochromically displaced. The observed changes are due to differences in the geometries of the compounds in question, as indicated by the fact that the introduction of a tetramethylene bridge into compound VIII disrupts the coplanarity of the chromophoric system. This interpretation is supported by the results of x-ray structure analysis for cis- and trans-N-carbamoyl-2-phenyl-7-benzylidene-hexahydroindazole [4], according to which the fragment C=C–C=N is twisted by 30-40°, and the phenylbenzylidene fragment deviates from the plane of the double bond as a consequence of steric repulsion with the hydrogen atoms at $C_{(6)}$.

The luminescence properties of the pyrazolines that we obtained exhibit certain specific features. The above-noted disruption of coplanarity of the main chromophoric system of these compounds leads to high Stokes shifts. Thus, upon annelation (change from compound VIII to compound IIa), we observe a drop of intensity of the fluorescence bands and an increase of the Stokes shift from 5040 to 8280 $cm^{-1}$. The fluorescence band undergoes a greater upfield shift in comparison with the corresponding absorption band. Also, the introduction of a second phenyl group into the thiazole ring (Va) results in an additional increase of the Stokes shift, indicating participation of the phenyl radical in process of change in molecular geometry and excitation of the state. The source of these changes, in our opinion, may be related to a difference in the degree of coplanarity of the absorbing and emitting molecules; i.e., the compaction of the chromophoric system that takes place during the lifetime of the excited state will lower the energy of the equilibrium excited fluorescent state. The introduction of either electron-donor or electron-acceptor substituents results in a reduction of the quantum yield.

## EXPERIMENTAL

The PMR spectra of compounds I-VI were taken on a Bruker WM-250 spectrometer in $CDCl_3$, with HMDS as an internal standard. The UV spectra were measured in dioxane on a Specord M-40 spectrophotometer, the fluorescence spectra in dioxane on a Hitachi F-4010 spectrofluorimeter. The purity of the products was monitored by TLC on Silufol UV-254 plates, in either toluene or 9:1 toluene/alcohol.

**2-Thiocarbamoyl-3-phenyl-7-benzylidene-3,3a,4,5,6,7-hexahydroindazole (Ia)** was obtained in accordance with [4], compounds Ib-d similarly.

**2-(4'-Arylthiazolyl)-3-aryl-7-arylidene-3,3a,4,5,6,7-hexahydroindazoles (II-IV).** To a mixture of 5 mmoles of the thioamide (Ia-c) in 30 ml of ethanol, 5.5 mmoles of the appropriate substituted ω-bromoacetophenone was added; the mixture was refluxed for 3-4 h until the original thioamide had completely disappeared from the reaction mixture (as indicated by TLC), and was then left to cool. The resulting precipitate was filtered off and crystallized from alcohol or toluene. The characteristics of the products are listed in Tables 1 and 2.

**2-(4',5'-Diphenylthiazolyl)-3-aryl-7-arylidene-3,3a,4,5,6,7-hexahydroindazoles (V-VII)** were obtained analogously. The mixtures of isomers were separated by chromatography in a column with $SiO_2$ (eluent $CHCl_3$).

This research was performed with support from the International Soros Program in the Field of Exact Sciences, International Fund Vidrogennia, Grant SPU 043046.

## REFERENCES

1. J. Krapcho and C. F. Turk, J. Med. Chem., **22**, 207 (1979).
2. A. A. Khalaf, A. K. El-Shafei, and A. M. El-Sayed, J. Heterocycl. Chem., **19**, 609 (1982).
3. M. S. Puar, G. C. Rovnyak, A. I. Cohen, and B. Toeplitz, J. Org. Chem., **44**, 2513 (1979).
4. T. Lorand, D. Szabo, A. Foldesi, L. Parkanyi, G. Kalman, and A. Neszmelyi, J. Chem. Soc., Perkin Trans. 1, No. 3, 481 (1985).
5. A. Hassner and M. Michelson, J. Org. Chem., **27**, 3974 (1962).
6. A. Hassner and T. S. Mead, Tetrahedron, **20**, 2201 (1964).
7. B. H. Chase and J. M. Evans, J. Chem. Soc., No. 12, 4825 (1964).