TETRAZOLE DERIVATIVES.

XX.* INVESTIGATION OF THE SYNTHESIS AND TRANSFORMATIONS OF THE 1-(1-METHYL-5-TETRAZOLYL)-3,5-DIPHENYLVERDAZYL LEUCO BASE

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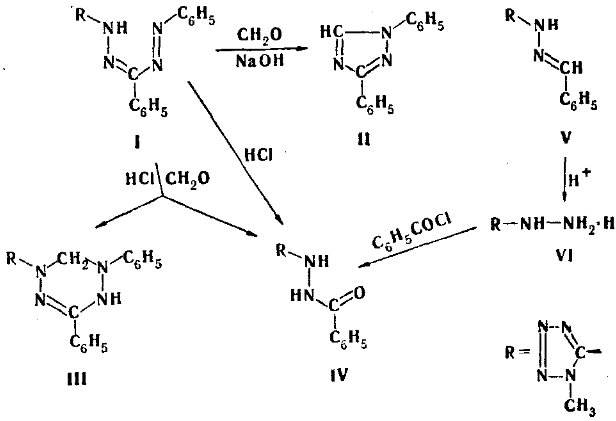
The corresponding leucoverdazyl and 1-methyl-5-β-benzoylhydrazidotetrazole are formed in the reaction of 1-(1-methyl-5-tetrazolyl)-3,5-diphenylformazan with formaldehyde in acidic media. 1,3-Diphenyl-1,2,4-triazole is formed when the reaction is carried out in alkaline media. According to the PMR spectral data, prototropic tautomerism is characteristic for the leucoverdazyl. The verdazyl radical derivative has the ability to undergo recyclization with conversion of the tetrazine ring to a triazole ring either spontaneously or when it is heated.

The possibility of preparation of the 1-(1-methyl-5-tetrazolyl)-3,5-diphenylverdazyl leuco base (III) by methylation of the corresponding formazan (I) with dimethyl sulfate in dimethylformamide (DMF) has been demonstrated [2]. However, the yield of leucoverdazyl III in this synthesis does not exceed 31% because of a side reaction involving methylation of the formazan at the 4-N atom of the tetrazole ring.

In the present research we studied the possibility of preparation of leucoverdazyl III by reaction of formazan I with formaldehyde. It was found that not even traces of leucoverdazyl III are formed when this reaction is carried out in an aqueous alkali medium over the investigated range of temperatures (0-50°C). 1,3-Diphenyl-1,2,4-triazole (II) and an unidentified compound with mp 183°C were isolated from the reaction mixture. The reaction takes place extremely slowly: formazan I is consumed completely at 18-20°C only after 13-14 days.

It should be noted that the formation of II [1, 3] or its derivatives [3] as side products was observed in the synthesis of other verdazyls via a similar scheme.

The effect of the steric hindrance created by the methyl group is in all likelihood exerted in the course of the reaction under consideration. In fact, the corresponding leucoverdazyls are obtained in good yields in a similar reaction when there is no methyl group in the tetrazolyl-containing formazan or when the methyl group is attached to the 2-N atom of the tetrazole ring [1, 4].



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*See [1] for communication XIX.

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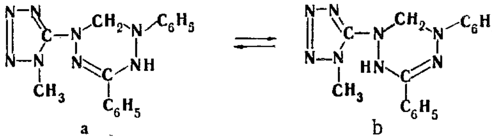
The reaction of formazan I with formaldehyde in an acidic alcohol medium proceeds even more slowly (30 days) and leads to the formation of leucoverdazyl III in low yield. In addition, a side product, for which the 1-methyl-5-β-benzoylhydrazidotetrazole structure (IV) was established, was isolated from the reaction mixture. This product was identical to the compound obtained by alternative synthesis via the following scheme: hydrolysis of hydrazone V by the method in [5] gave 1-methyl-5-hydrazinotetrazole hydrochloride (VI), which was subjected to benzoylation in a slightly alkaline medium.

The formation of hydrazide IV during the preparation of leudoverdazyl III is due to the accompanying hydrolytic cleavage of formazan I. It was found that this reaction proceeds particularly readily in acetone, in which formazan I is converted to hydrazide IV in almost quantitative yield after 4 h in the presence of hydrochloric acid. One should note the atypical character of the cleavage of I. In acidic media formazans usually undergo cyclization to various condensed heterocyclic derivatives [6, 7].

Attempts to synthesize the leucoverdazyl by reaction of formazan I with formaldehyde in DMF in the presence of $KHSO_4$ by the method in [3] were unsuccessful.

According to the PMR spectral data, leucoverdazyl III displays prototropic tautomerism. Thus doubling of the signals of the methyl and NH groups at **4.03** and 4.12 and 9.10 and **9.36** ppm (the more intense band is given in boldface), respectively, is observed in the spectrum of III in DMSO. The signal of the methylene group (5.20 ppm) is appreciably broadened on the strong-field side in the presence of a base. From the ratio of the intensities of the signals of the CH_3 group the percentages of the tautomers are 13 and 87%.


a b

Gradual merging of the split signals of the CH_3 group and contraction into a single narrow singlet of the band of the CH_2 group as a consequence of acceleration of exchange between tautomeric forms *a* and b is observed in the case of successive acidification of a solution of a sample in DMSO with acetic acid or, better yet, trifluoroacetic acid. The predominance of one of the tautomers becomes complete in deuterochloroform solution. The signals of the protons of the methyl, methylene, and NH groups appear in the PMR spectrum in the form of narrow singlets at 4.04, 5.16, and 6.71 ppm, respectively. When the solution is acidified with acetic acid, the signal of the NH group is broadened somewhat and shifted to weak field, while the remaining signals do not change.

The greater shift of the tautomeric equilibrium to favor one of the forms as compared with the shift observed for the 2-methyl-5-tetrazolyl-containing analog, for which the ratio of the tautomeric forms in DMSO amounts to 48 and 52%, as compared with 62 and 38% in $CDCl_3$ [1], is evidently a consequence of the great electron-acceptor character of the 1-methyltetrazolyl substituent [8], which intensifies the nonequivalence of the 2-N and 4-N atoms of the tetrazine ring. Taking into account the data on the structure of the 1-(p-nitrophenyl)-3,5-diphenylverdazyl leuco base [9], for which it was been established that the hydrogen is attached to the 4-N atom, one may assume that the equilibrium is shifted to favor tautomer *a* in the case of leuco base III.

The absorption of the NH group in the IR spectrum of III in chloroform appears at 3371 cm^{-1} in the form of a narrow intense band (at 3370 cm^{-1} in the case of CCl_4). However, in the crystalline state the absorption of the NH group is found at a considerably lower frequency (3170 cm^{-1}); this is due to participation of this group in intermolecular association. It is noteworthy that in the case of crystals of other leucoverdazyls [1, 2, 4] the NH group has free nonassociated character, if one judges from the position of its IR band (3320-3350 cm^{-1}).

Verdazyl radical VII displays an unusual ability to readily undergo conversion to a compound with empirical formula $C_{16}H_{14}N_8$ (VIII).* The conversion may proceed spontaneously: when a sample of verdazyl radical VII is stored for 3 months at room temperature, it is decolorized and undergoes conversion to VIII and leucoverdazyl III.

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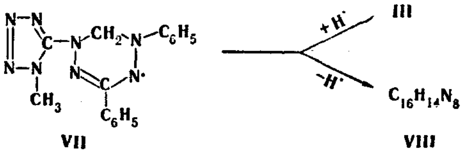
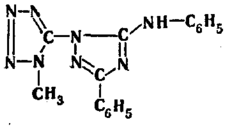
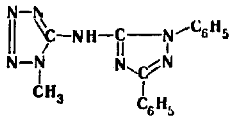
*See [10] for a preliminary communication regarding this.



It is important to note that under the same conditions 1-(2-methyl-5-tetrazolyl)- and 1-(5-tetrazolyl)-3,5-diphenylverdazyl radicals [1, 4] do not undergo changes in the course of a year or more. The same compounds (III and VIII) are obtained when crystalline verdazyl radical VII is heated at 100°C for 6 h or when it is refluxed in acetone. It was found that in this case the tetrazine ring undergoes contraction to a triazole ring, as occurs when the triphenylverdazyl radical is heated to 200°C or when it is refluxed in benzene for 4 days [11].



VIII a



VIII b

Signals at 3.80 (3H, s, CH_3), 7.34-8.10 (10H, m, C_6H_5), and 10.62 ppm (1H, s, NH) are observed in the PMR spectrum of VIII in DMSO. Bands at 3256, 3230, and 3180 cm^{-1} (νNH) are observed in the IR spectrum of VIII in CCl_4. Absorption of the NH groups was not observed under the conditions previously used for the recording of the IR spectrum (of crystalline VIII), and this served as a basis for the erroneous judgment [10] regarding the structure of this compound.

The recyclization of verdazyl radical VII is possible through cleavage of both the (1-N)—(2-N) and (4-N)—(5-N) bonds; additional studies to establish which of the two possible isomers (VIIIa and VIIIb) is formed are therefore necessary.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in DMSO and deuterochloroform were recorded with a Perkin—Elmer R-12B spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets and saturated solutions of the compounds in $CHCl_3$ and CCl_4 (layer thickness 2 cm) were recorded with a UR-20 spectrometer. The UV spectra were measured with an SF-4A spectrophotometer. The melting points were determined with a PTP-1 apparatus. The individuality of the compounds was monitored by thin-layer chromatography (TLC) on Silufol in a chloroform—acetone system (100:5).

Reaction of Formazan I with Formaldehyde in an Alkaline Medium. A solution of 1.8 g (5.9 mmole) of formazine I and 2.5 ml (31 mmole) of 37% formaldehyde in 60 ml of 1% NaOH was maintained at 18-20°C for 14 days, and the resulting colorless precipitate was removed by filtration, washed with water, and recrystallized from 50 ml of ethanol to give 0.3 g of an unidentified substance with mp 183°C. The alcohol filtrate was concentrated, and the residue was recrystallized from heptane to give 0.6 g (46%) of 1,3-diphenyltriazole with mp 79-80°C (mp 80-81°C [1] and 82.5-83°C [12]).

Reaction of Formazan I with Formaldehyde in an Acidic Medium. A mixture of 5.6 g (18.3 mmole) of formazan I, 10 ml (127 mmole) of 37% formaldehyde, 2 ml of concentrated HCl, and 200 ml of ethanol was maintained at 18-20°C for 30 days, and the resulting solution was concentrated. The residue was treated with 50 ml of hot water, and the aqueous mixture was filtered to give a resinous substance (A). Purification of this substance by refluxing in 40 ml of ethanol with 2 g of fine-fibered asbestos gave 1 g (17%) of leucoverdazyl III with mp 157-158°C (mp 158°C [2]). According to the results of a mixed-melting-point determination and the IR spectra, the product was identical to a genuine sample [2].

After separation of substance A, 0.9 g (21%) of 1-methyl-5-β-benzoylhydrazidotetrazole (IV), with mp 144-145°C (colorless elongated plates from 50% ethanol) (mp 149-150°C [13]), crystallized out from the aqueous filtrate in the course of 24 h. IR spectrum: 1675 cm^{-1} (C=O). PMR spectrum (in DMSO): 3.82 (s, CH_3), 7.44-7.96 (m, C_6H_5), 9.27 (s, α-NH), and 10.72 ppm (s, β-NH). Found: C 45.7; H 5.0; N 35.5%. $C_9H_{10}N_6O \cdot H_2O$. Calculated: C 45.6; H 5.0; N 35.6%.

Alternative Synthesis of 1-Methyl-5-β-benzoylhydrazidotetrazole (IV). A 1.8-ml (15 mmole) sample of benzoyl chloride was added to a solution of 1.5 g (15 mmole) of 1-methyl-

5-hydrazinotetrazole hydrochloride [5] in 20 ml of 10% Na_2CO_3 solution, and the mixture was stirred for 3 h. It was then filtered, and the solid material was washed by suspension in benzene to give 2.7 g (76%) of IV with mp 143-144°C (from 50% ethanol). According to the IR spectra, the product was identical to the above-described IV; no melting-point depression was observed for a mixture of this product with a sample of the latter.

Hydrolysis of Formazan I. A solution of 0.5 g (1.6 mmole) of formazan I, 1 ml of concentrated HCl, and 26 ml of acetone was maintained at room temperature for 4 h, after which the precipitate was removed by filtration to give 0.35 g (91%) of hydrazide IV with mp 144-145°C.

Conversion of Verdazyl Radical VII. A solution of 0.6 g (1.88 mmole) of verdazyl radical VII in 35 ml of acetone was refluxed for 5 h, and the precipitated VIII (0.27 g) was removed by filtration. The filtrate was concentrated, the residue was treated with 10 ml of 1% NaOH, and the mixture was filtered to give 0.2 g of leucoverdazyl III with mp 157-158°C (from ethanol). Acidification of the alkaline filtrate with concentrated HCl and workup of the mixture gave an additional 0.07 g of VIII (for an overall yield of 57%) with mp 194.5-195°C (colorless needles from ethanol). UV spectrum (in ethanol): λ_{max} 290 nm (log ε 4.41). IR spectrum (KBr): 1632, 1550, 1465, 1410, 1150, 970, 765, and 695 cm^{-1}. PMR spectrum (in CF_3COOH): 3.56 (3H, s, CH_3) and 7.12-7.63 ppm (10H, m, C_6H_5). Found: C 60.1; H 4.6; N 35.0%; M 337 (by cryoscopy in camphor). $C_{16}H_{14}N_8$. Calculated: C 60.4; H 4.4; N 35.2%; M 318.

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