TETRAZOLE DERIVATIVES.
25.* INVESTIGATION OF THE SYNTHESIS OF 1-(5-TETRAZOLYL)-3,5-DIPHENYLLEUCOVERDAZYL. STRUCTURE AND SOME PROPERTIES OF THE ACCOMPANYING PRODUCT — 1,3,7,9-TETRAPHENYL-5-OXO-5H-1,2,4-TRIAZOLO[3',4':5,1]IMIDAZO[4,3-c]-1,2,4-TRIAZOLE

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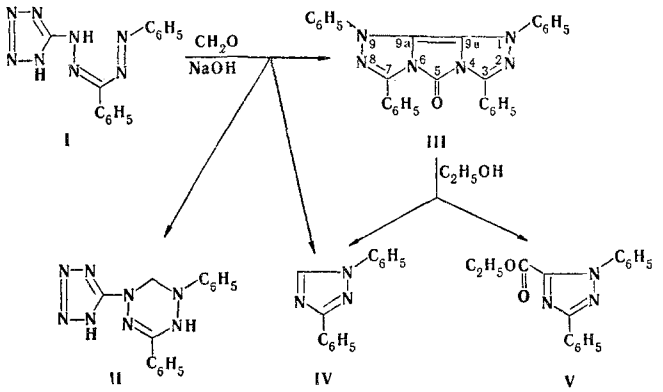
In the reaction of 1,3-diphenyl-5-(5-tetrazolyl)formazan with formaldehyde, in addition to a leucoverdazyl, one can obtain 1,3-diphenyl-1,2,4-triazole and 1,3,7,9-tetraphenyl-5-oxo-5H-1,2,4-triazolo[3',4':5,1]imidazo[4,3-c]-1,2,4-triazole. The structure of the latter was established from data from the mass spectrum and the ^{1}H and ^{13}C NMR, UV, and IR spectra, as well as from the products of alcoholysis of this compound, which leads to 1,3-diphenyl-1,2,4-triazole and 1,3-diphenyl-5-carbethoxy-1,2,4-triazole. According to the data from the PMR spectra, the leucoverdazyl displays prototropic tautomerism due to the NH proton of the tetrazine ring.

Tetrazolyl-containing leucoverdazyls are promising antibiotics [2]. The most accessible compound of this type is 1-(5-tetrazolyl)-3,5-diphenylleucoverdazyl (II), which is readily obtained in the reaction of 1,3-diphenyl-5-(5-tetrazolyl)formazan (I) with formaldehyde in an alkaline medium [3]. We observed that, in addition to leucoverdazyl II in this reaction one can also obtain compounds for which we established 1,3,7,9-tetraphenyl-5-oxo-5H-1,2,4-triazolo[3',4':5,1]imidazo[4,3-c]-1,2,4-triazole (III) and 1,3-diphenyl-1,2,4-triazole (IV); the course of the reaction depends substantially on the amount of formaldehyde. As the amount of formaldehyde in the reaction mixture is increased, the yield of leuco base II increases, while the yield of III decreases (Table 1). Triazole derivative IV accompanies III, and its yield amounts to no more than one fifth of the yield of III.



The structure of III was established on the basis of the following spectral data. By means of high-resolution mass spectrometry (HRMS) we established the empirical formula $C_{29}H_{20}N_6O$ (determined: 468.1682; calculated: 468.1698). The use of the defocusing method [4] and recording of the spectrum of the field desorption of III [the M^+ (m/e 468) and $[M + 1]^+$ (m/e 469) ions were recorded] demonstrated that the ion peak with mass 468 is

*See [1] for Communication 24.

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TABLE 1. Yields of II and III

I:CH_2O molar ratio	Yield, %	
	II	III
1,0 : 2,5*	41	19
1,0 : 2,8	56	12
1,0 : 3,2	62	11
1,0 : 3,6	65	10
1,0 : 4,1	70	3
1,0 : 5,6	71	Traces

*Unchanged formazan I remains in the reaction mixture.

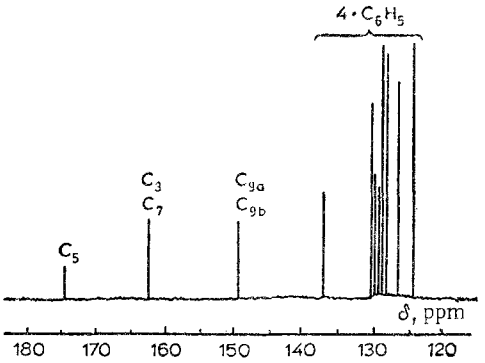
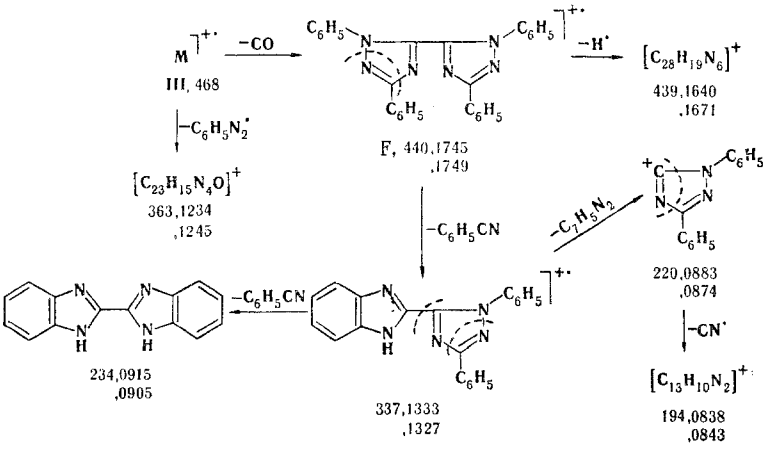


Fig. 1. ^{13}C NMR spectrum of III in $CHCl_3$—$CDCl_3$ (1:1).

the molecular ion. The IR spectrum of III contains an intense $\nu_{C=O}$ absorption band at 1700 cm^{-1}. The PMR spectrum contains two groups of signals of aromatic protons, viz., complex multiplets at 7.38-7.61 and 8.10-8.23 ppm.

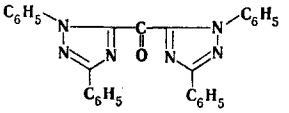
Eleven signals at 120-180 ppm are observed in the ^{13}C NMR spectrum of III (Fig. 1). The NMR spectrum obtained by the technique of partial intensification of the resonance signals of the ^{13}C atoms due to the Overhauser effect with retention of the true values of the spin—spin coupling constants (SSCC) $^{n}J_{^{13}C-H}$ shows that five of them correspond to the resonance of quaternary carbon nuclei, while six correspond to tertiary carbon nuclei. The ratio of the integral intensities of the signals indicates symmetry of the molecule corresponding to structure III: the symmetrical orientation of the phenyl substituents taken in pairs, the existence of two pairs of symmetrical carbon nuclei in the heterocyclic part of the molecule, and the position of the carbonyl carbon atom on the axis of symmetry of the molecule. The magnitude of the chemical shift of the signal of the carbonyl group (174.14



ppm) and the absence of an SSCC in the spectrum obtained by the technique of partial intensification of the resonance signals of the ^{13}C carbons confirm the position of the carbonyl carbon atom between two nitrogen atoms [5]. In the spectrum obtained by the same recording technique the signal at 162.36 ppm is a triplet with $^{3}J_{^{13}C-H} = 4.4$ Hz, while the signal at 149.86 ppm is a singlet; this makes it possible to assign them to the resonance of paired symmetrical C_3 and C_7 and C_{9a} and C_{9b} nuclei, respectively. The signals of the carbon nuclei that are included in the phenyl residue have chemical shifts of 137.63 (quaternary), 129.90 and 129.85 (quaternary), and 129.49, 129.17, 128.54, 126.90, and 124.94 ppm.

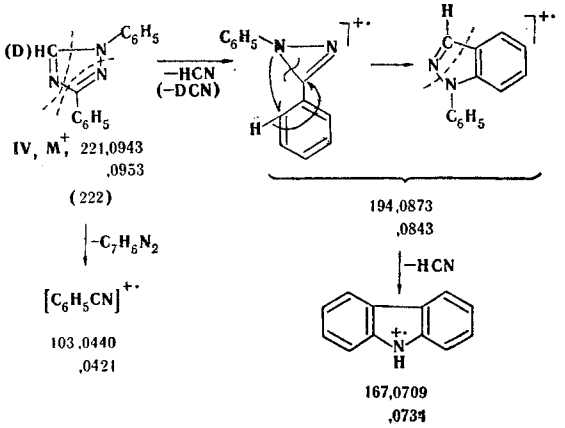
The character of the fragmentation of M^+ confirms the structure of III. In the first stages of the fragmentation a CO particle (the F ion) is ejected; this is characteristic for cyclic and heterocyclic ketones (for example, for quinones [6], pyrazolones [7], uracils [8], etc.). In addition, a $C_6H_5N_2$ particle is eliminated (specific fragmentation for 1,2,4-triazoles [9]) from M^+. The subsequent fragmentation of the F ion takes place with the successive elimination of two C_6H_5N molecules. The sequence of the fragmentation of M^+ and the fragment ions was established from the spectra of the metastable ions by the DADI technique [10].*

An alternative structure for III could be the structure of the corresponding ketone with the same empirical composition.



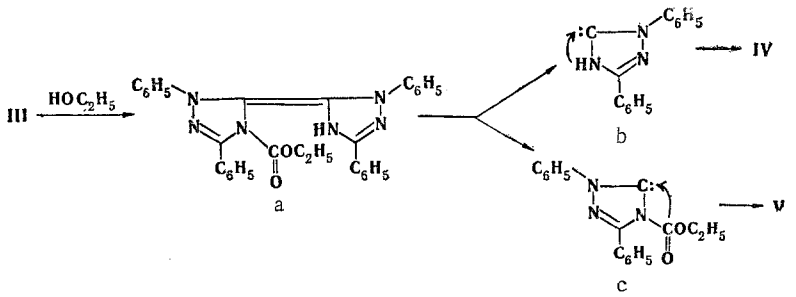
However, it is refuted both by data from mass spectrometry (there is no characteristic (for ketones) α cleavage of the bond relative to the carbonyl group) and by data from the ^{13}C NMR spectrum (the chemical shift of the carbonyl carbon of the ketones is greater than 190 ppm) [11]. Nevertheless, starting from the assumption regarding the ketone structure of the substance we attempted to obtain the corresponding oxime by heating the investigated compound in alcohol with hydroxylamine hydrochloride. Instead of the expected oxime, as a result of the reaction we obtained two products, which were identified as 1,3-diphenyl-1,2,4-triazole (IV) and 1,3-diphenyl-5-carbethoxy-1,2,4-triazole (V). The formation of these substances proved to be a consequence of the facile alcoholysis of III. Thus when it is refluxed in ethanol for 1.5 h, the same IV and V are obtained.

Performance of alcoholysis in deuterated alcohol (C_2H_5OD) and a subsequent mass-spectral study of the compounds obtained showed that deuterium is absent in V but is present in IV at the C_5 atom. This follows from the character of the fragmentation observed in the mass spectrum:



The experimental data obtained make it possible to assume that the alcoholysis of III proceeds via the following mechanism:

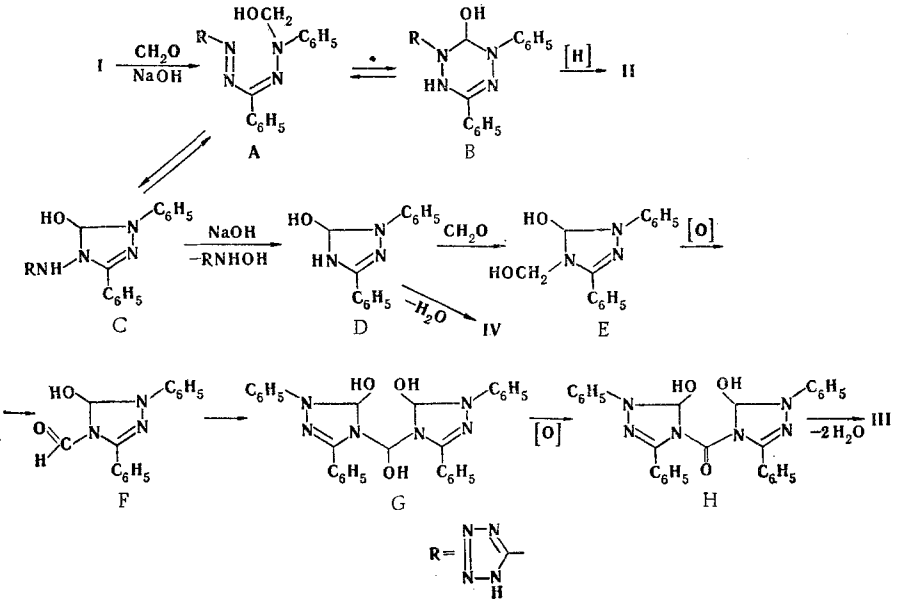
*Here and subsequently, the numbers under the formulas designate the precise mass number determined experimentally by means of high-resolution mass spectrometry, and the numbers given below these numbers in parentheses are the calculated mass numbers for the given empirical compositions.



Nucleophilic addition of a molecule of ethanol with cleavage of the amide C–N bond leads to the formation of ethyl carbamate derivative a, which dissociates to give carbenes b and c. It is well known that this sort of dissociation of the ethylene bond occurs readily in the case of 2,2-bis(1,3-diphenylimidazolidin-2-ylidene) and its derivatives [12]. Carbenes b and c subsequently undergo a 1,2-sigmatropic shift and are converted to products IV and V.

Compounds IV and V to a certain extent may serve as "model" compounds for the assignment of some spectral characteristics of the new heterocyclic III system. Thus the IR spectrum of III contains a very intense absorption band at 900 cm^{-1}, which is absent in the spectra of "models" IV and V. It can be assigned to the skeletal vibrations of the central imidazolone ring [13]. As compared with IV and V, a long-wave band, which is due to a conjugated system of three heterorings [λ_{max} (log ε): III, 245 (4.32) and 325 nm (3.48); IV, 262 nm (4.20); V, 240 nm (4.47)], appears in the electronic spectrum of III.

The mechanism of the synthesis of II-IV can be represented as follows. Hydroxymethyl derivative A, which undergoes cyclization in an alkaline medium to give B and C is formed in the reaction of formazan I with formaldehyde. Hydroxytetrazine derivative B is reduced to leucoverdazyl II.



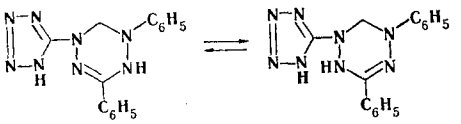
It is appropriate here to note the analogy with 6-aminoverdazyls, which are capable of undergoing reduction at the exocyclic C–N bond, as well as decyclization with cleavage of the endocyclic N_1–C_6 bond [14].

In all likelihood, the reduction of B is realized by means of formaldehyde, which may explain the necessity for the consumption of 2 moles of CH_2O per mole of formazan I. Under the influence of alkali, triazoline derivative B undergoes fragmentation at the exocyclic N–N bond. It is known that this sort of fragmentation at the N–N bond in some cases proceeds quite readily [15]. Compound D subsequently undergoes dehydration to give triazole IV or undergoes a chain of transformations through derivatives E-H to give III. It should be noted that all of the intermediate steps in the formation of III and IV proceed under homogeneous conditions and that only the final products precipitate from the reaction mixture as a consequence of their insolubility in aqueous alkali. The observed decrease in

the yields of III and IV with a simultaneous increase in the yield of leucoverdazyl II when the amount of formaldehyde used in the reaction is increased may be associated with an increase in the rate of reduction of the B ring due to the increased formaldehyde concentration.

The reaction of other formazans with formaldehyde in an alkaline medium can also be represented by a similar scheme; the probability of transformations via the A → B → D pathway up to complete prevalence of this reaction pathway increases in this case as the electron-acceptor character of the substituent attached to the N_1 or C_3 atom of the formazan grouping increases. Thus in the reaction of 1,3-diphenyl-5-(1-methyl-5-tetrazolyl)-formazan* with formaldehyde in an aqueous alkali medium, as demonstrated in [16], one does not observe even traces of the leucoverdazyl, whereas the products of the synthesis are triazole IV and a substance that proved to be identical to III. The formation of triazole derivatives of the IV type was observed in the reaction with formaldehyde and a number of other formazans that contain acceptor substituents [17, 18]. It is important to note that triazole derivatives are not obtained in the case of other methods for the synthesis of verdazyls that exclude the use of formaldehyde and alkali [19].

According to the data from the PMR spectrum, leuco base II, like its analogs that are methylated in the tetrazole ring [16, 18], displays prototropic tautomerism. Doubling of the signals of the methylene group and the NH group of the tetrazine ring at 5.17 and 5.29 ppm and at 9.21 and 9.40 ppm (the more intense band is printed in boldface type) is observed in dimethyl sulfoxide (DMSO). The signal of the tetrazole proton is shifted to weak field (15.50 ppm) and is broadened markedly.



T_1 T_2

When two drops of water are added to the solution, one observes merging of the split signals, which is a consequence of acceleration of exchange between the tautomeric T_1 and T_2 forms. From the ratio of the intensities of the split signals the percentages of tautomers T_1 and T_2, with allowance for the data in [16, 18, 20], are 81 and 19%, respectively. The position of the tautomeric equilibrium of leucoverdazyl II is comparable to the position of the analog that contains a 1-methyl-5-tetrazolyl ring (87 and 13% [16]) and differs from the position of the isomer that contains a 2-methyltetrazolyl ring (48 and 52% of forms of the T_1 and T_2 type, respectively [18]); this constitutes evidence in favor of the 1-H structure of the tetrazole ring in II.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were measured with an SF-4A spectrophotometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Perkin–Elmer R-12B and Brucker WH-90 spectrometers with tetramethylsilane (TMS) as the internal standard. The ^{13}C NMR spectra of solutions in $CHCl_3$–$CDCl_3$ (1:1) were recorded with a Brucker WP-80 DS spectrometer (West Germany) with an operating frequency of 20.115 MHz. The conditions for recording the spectra with broad-band suppression with respect to the protons were as follows: The volume of the memory for storage and reproduction of the spectra was 8 K, the pulse duration was 1 μsec, the interval of time between scannings was 4 sec, the number of storages was 3000, and the operating resolution was 0.45 Hz (0.023 ppm). The chemical shifts were reckoned from the signal of $CHCl_3$ and were rescaled to the δ scale relative to TMS from the formula $\delta_{TMS} = \delta_{CHCl_3} + 77.20$ ppm. The mass spectra were obtained with a Varian model MAT-311A spectrometer under standard conditions: The accelerating voltage was 3 kV, the cathode emission current was 300 μA, the ionizing voltage was 70 eV, and the sample vaporization time was 100–140°C. The high-resolution mass spectra were obtained at a resolution of $M/\Delta M = 20{,}000$ (with polyphosphoric acid as the standard). The

*The greater electron-acceptor character of the 1-methyltetrazolyl substituent as compared with the tetrazolyl anion, which is present as a substituent in I in an alkaline medium, is obvious.

individuality of the compounds was monitored by TLC on Silufol; the R_f values are presented for the acetone—CCl_4 system (1:3).

Reaction of Formazan I with Formaldehyde. A solution of 6 g (20.5 mmole) of formazan I and 4.2 ml (57.4 mmole) of 37% formaldehyde in 180 ml of 1% NaOH was maintained at 18-20°C without access to the air for 24 h (the reaction was complete in 3 h, but the standing time was increased for coagulation of the very fine precipitate). The decolorized reaction mixture was filtered, and the precipitate was washed with water, dried, and suspended in 10 ml of ethanol and filtered to give 0.6 g (12%) of III with mp 183-184°C (long colorless needles from ethanol) and R_f 0.74. IR spectrum: 3080, 1700, 1602, 1505, 1450, 900, 700, 735, 700 cm^{-1}. Mass spectrum,* m/e (%): 64 (11.4), 65 (4.9), 77 (18.4), 91 (100.0), 92 (8.0), 103 (4.3), 104 (4.1), 167 (5.9), 194 (30.6), 220 (4.3), 234 (6.4), 336 (7.2), 337 (7.2), 363 (6.9), 439 (28.9), 440 (61.0), 468 (48.0), 469 (15.0). Found: C 73.9; H 4.2; N 17.7%. $C_{29}H_{20}N_6O$. Calculated: C 74.3; H 4.3; N 17.9%. The compound was readily soluble in benzene, heptane, and chloroform, only slightly soluble in alcohol and acetone, and insoluble in water. It was recrystallized satisfactorily from glacial acetic acid.

The alcohol filtrate obtained in the isolation of III was evaporated to dryness, and the residue was extracted with 10 ml of boiling heptane. The extract was evaporated to half its original volume to give 0.1 g (2%) of triazole IV with mp 80-81°C (from 50% ethanol) and R_f 0.45. According to the data in [21, 22], this compound had mp 81-83 and 78-80°C, respectively. The IR, UV, and PMR spectra of IV were in agreement with those described in [22].

The aqueous alkaline filtrate obtained in the isolation of the mixture of III and IV was acidified with concentrated HCl, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from benzene—ethanol (9:1) to give 3.5 g (56%) of leucoverdazyl II with mp 181-182°C (dec., from ethanol) (according to the data in [3], this compound had mp 180.5-182.5°C). The yields of II and III in the case of a different amount of formaldehyde with retention of the conditions and amounts of the rest of the reagents are presented in Table 1.

Alcoholysis of III. A 0.5-g sample of III was refluxed in 25 ml of ethanol for 2 h, after which the resulting solution was evaporated to dryness, and the residue was recrystallized from heptane to give 0.1 g (32%) of carbethoxytriazole V with mp 114.5-115.5°C (mp 118.5-119.5° [21]) and R_f 0.59. IR spectrum: 1742 cm^{-1} (ν_{CO}). PMR spectrum (in CCl_4), δ: 1.35 (3H, t, J = 6 Hz, CH_3), 4.27 (2H, q, J = 6 Hz, CH_2), and 7.25-8.20 ppm (10H, m, C_6H_5). Mass spectrum, m/e (%): 77 (19.2), 84 (17.1), 91 (100.0), 118 (90.7), 194 (18.1), 221 (35.1), 248 (7.8), 293 (88.9). Found: C 69.9; H 5.4; N 14.6%; M^+ 293.1163 (according to data from high-resolution mass spectrometry). $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.2; N 14.3%; M 293.1164.

The filtrate (the heptane solution) obtained after isolation of V was concentrated, and the residue was recrystallized from ethanol to give 0.2 g (83%) of triazole IV with mp 80-81°C. The product was identical with respect to its IR spectrum to triazole IV described in the preceding synthesis.

The alcoholysis of III by means of C_2H_5OD and the isolation of IV and V were carried out similarly. According to the data from the mass spectrum, 88.4% of the deutero derivative was present in the resulting IV.

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*The peaks of ions with intensities ≥ 3% of the maximum peak in the mass spectrum are indicated.

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