BISINDOLES.

20.* SYNTHESIS OF 3H,8H-INDOLO[4,5-e]- AND -[5,4-e]INDOLE SYSTEMS

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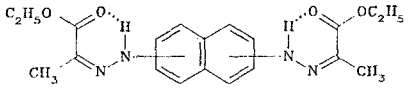
634:543.422'51

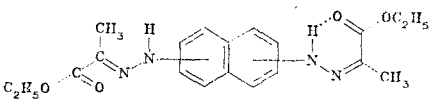
New heterocyclic systems, viz., 3H,8H-indolo[4,5-e]indole and 3H,8H-indolo-[5,4-e]indole, which were also obtained from the corresponding pyruvic acid dihydrazones, were synthesized by cyclization of ethyl pyruvate 2,7- and 2,6-naphthylenedihydrazones and subsequent saponification and decarboxylation of the cyclization products. The syn-syn, syn-anti, and anti-anti forms of the dihydrazones were isolated and characterized.

The synthesis of new structural isomers of the previously synthesized 1H,6H-indolo[7,6-g]-indole [2], viz., unsubstituted 3H,8H-indolo[4,5-e]indole (XI) and 3H,8H,indolo[5,4-e]indole (XII) and some of their derivatives, by Fischer cyclization of pyruvic acid 2,7- and 2,6-naphthylenedihydrazones (III, IV) and ethyl pyruvate 2,7- and 2,6-naphthylenedihydrazones (V, VI).

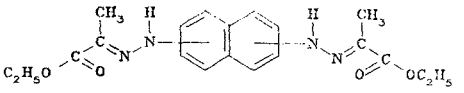
Dihydrazones III-VI were obtained from 2,7- and 2,6-naphthylenedihydrazine dihydrochlorides (I and II) [3] in aqueous solutions. Separation of the mixtures of dihydrazones V (2, 7) and VI (2, 6) into individual isomers was accomplished by column chromatography on silica gel. The syn-syn (Va, VIa), syn-anti (Vb, VIb), and anti-anti (Vc, VIc) forms of the isomers were isolated.



Va, VIa



Vb, VIb



Vc, VIc

It is known [4, 5] that the difference in the physical properties of the syn and anti forms of hydrazones as a consequence of the formation of chelate structures with a hydrogen bond leads to changes in the UV, IR, and PMR spectra of the isomers. A comparison of the PMR spectra of dihydrazones Va-c and VIa-c (Table 1) shows that the signals of the NH protons of isomers Va and VIa are shifted to significantly weaker field as compared with the analogous signals in the spectra of isomers Vc and VIc because of their participation in the formation of a strong intramolecular hydrogen bond (IHB), which is possible only in the case of a syn-syn orientation of the substituents. Two signals of NH protons and noncoincidence of the chemical shifts of the protons of the CH_3 and C_2H_5 groups in the 2,7 and 2,6 positions are observed in the PMR spectra of isomers Vb and VIb (Table 1); this indicates the nonsymmetrical character of the structure, i.e., the syn-anti orientation of these substituents.

Corresponding changes due to the formation of a hydrogen bond are also observed in the IR and UV spectra (Fig. 1) of dihydrazones V and VI.

*See [1] for Communication 19.

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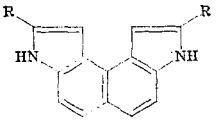
TABLE 1. PMR Spectra of Dihydrazones III-VI (ppm)

Compound	R	1H	3H	4H	NH	CH_3	CH_2—Et	CH_3—Et	J, Hz	Solvent
III	H	7,56 d	7,37 dd	7,63 d	9,7 s	2,08 s	—	—	J_{13}=2,0; J_{34}=8,4	d_6-DMSO 80°
IV	H		7,59[a]		9,65 s	2,06 s	—	—	—	d_6-DMSO 80°
Va	C_2H_5	7,34 d	7,17 dd	7,60 d	12,1 s;	2,18 s	4,25 q	1,35 t	J_{13}=1,5; J_{34}=8,4; J_{Et}=7,2	$CDCl_3$
Vb	C_2H_5	7,35 d	7,20 dd	7,62 d	12,1 s; 7,77 s	2,18 s; 2,12 s	4,25 q; 4,32 q	1,35 t; 1,39 t	J_{13}=2,2; J_{34}=8,6; J_{Et}=7,2	$CDCl_3$
Vc	C_2H_5	7,39 d	7,22 dd	7,63 d	7,85 s	2,13 s	4,33 q	1,39 t	J_{13}=2,0; J_{34}=8,6; J_{Et}=7,2	$CDCl_3$
VIa	C_2H_5	7,4—7,2		7,63 d	12,1 s	2,18 s	4,26 q	1,36 t	J_{34}=8,7; J_{Et}=7,2	$CDCl_3$
VIb	C_2H_5	7,55 s	7,39 d; 7,41 d	7,66 d; 7,69 d	12,1 s; 9,2 s	2,14 s; 2,12 s	4,24 q; 4,28 q	1,33 t	J_{34}=8,7; J_{78}=8,9; J_{Et}=7,1; J_{Et}=7,0	d_6-Acetone
VIc	C_2H_5	7,42 d	7,35 dd	7,65 d	7,72 s	2,11 s	4,31 q	1,38 t	J_{13}=1,5; J_{34}=9,0; J_{Et}=7,0	$CDCl_3$

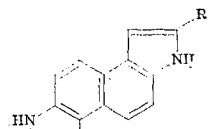
[a]An A_3 spectrum.

Dihydrazones III-VI cyclized in the form of mixtures of isomers. The best cyclizing agents were a mixture of glacial acetic and sulfuric acids for dihydrazones III and IV and ethyl polyphosphate (EPP) for dihydrazones V and VI.

The formation of six isomeric indoloindoles, viz., four symmetrical (two linear and two angular) and two unsymmetrical structures, is theoretically possible in the cyclization of dihydrazones III-VI, but we were able to isolate only one isomer.



VII, IX, XI



VIII, X, XII

The symmetrical angular structure of the isolated indoloindoles XI and XII (R = H) was confirmed by a study of the PMR spectra of both indoloindoles XI and XII themselves and their diethoxycarbonyl (VII, VIII) and dicarboxy (IX, X) derivatives (Table 2). In the PMR spectra of VII-XII the chemical shifts of the protons attached to atoms located in identical positions of each indole ring are identical when identical substituents are attached to them as a consequence of the symmetrical character of the molecules. Angular attachment of the pyrrole rings in VII-XII is confirmed by the presence in the PMR spectra of ortho spin–spin coupling constants (SSCC) between the 4-H and 5-H protons of the naphthalene ring (Table 2). Unambiguous assignment of the signals of the 4-H and 5-H protons was possible owing to the appearance in the PMR spectrum of XI of long-range SSCC of the transoid type through five bonds [6].

The shift of the signal of the 1-H proton (XI, R = H) to weaker field as compared with the analogous signal of 1H,6H-indolo[7, 6-g]indole (6.61 ppm) [7] and indoloindole XII is explained by the spatial orientation of the 1-H and 10-H protons, in which the electron shells can undergo exchange coupling [8].

The mass-spectral fragmentation of 3H,8H-indolo[4,5-e]- and -[5,4-e]indole does not differ fundamentally from the scheme of the fragmentation of 1H,6H-indolo[7,6-g]indole [7]. Because of the monotypic character of the mass spectra of the isomeric indoloindoles we will present the fragmentation of only XI:*

$$M^+\ 206\ (100) \xrightarrow{-H} 205\ (24) \xrightarrow{-HCN} 178\ (10) \xrightarrow{-HCN} 151\ (10)$$

$$M^+\ 206\ (100) \xrightarrow{-C_7H_5N} 103\ (25)$$

Intense peaks at 261.8 and 271 and at 215 and 244 nm, respectively, as well as low-intensity bands at 301-322, 317, 333, and 348 nm, are observed in the absorption spectra of 3H,8H-indolo[4,5-e]indole and 3H,8H-indolo[5,4-e]indole. A comparison of the UV spectra of

*The m/z (%) values are given.

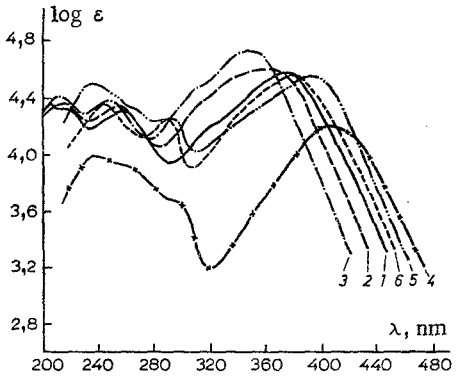


Fig. 1

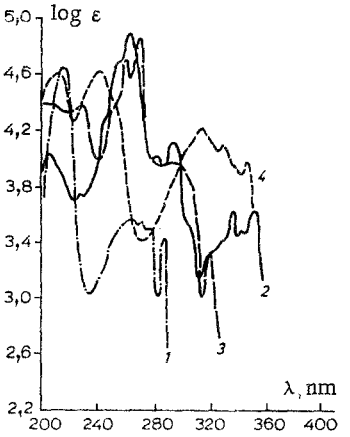


Fig. 2

Fig. 1. UV spectra: ethyl pyruvate 2,7-naphthylenedihydrazone: 1) syn-syn iosmer; 2) syn-anti isomer; 3) anti-anti isomer; ethyl pyruvate 2,6-naphthylenedihydrazone; 4) syn-syn isomer; 5) syn-anti isomer; 6) anti-anti isomer.

Fig. 2. UV spectra: 1) indole; 2) 1H,6H-indolo[7,6-g]indole; 3) 3H,8H-indolo[4,5-e]indole; 4) 3H,8H-indolo[5,4-e]indole.

TABLE 2. PMR Spectra of VII-XII in d_6-DMSO at 80°C (ppm)

Compound	R	1H	2H	3H	4H	5H	CH_2	CH_3	J, Hz
VII	$COOC_2H_5$	7,79 d	—	12,1s	7,52 d	7,75 d	4,40 q	1,41 t	$J_{13}=1,8$; $J_{45}=8,9$; $J_{Et}=7,1$
VIII	$COOC_2H_5$	7,67d	—	11,9 s	7,60[a] d	8,17[a] d	4,40 q	1,37 t	$J_{13}=2,2$; $J_{45}=8,9$; $J_{Et}=7,0$
IX	COOH	7,78 s	—	11,9s	7,50 d	7,73 d	—	—	$J_{45}=8,4$
X	COOH	7,62 s	—	11,8s	7,60[a] d	8,10[a] d	—	—	$J_{45}=8,6$
XI[b]	H	7,34 m	7,43 dd	10,5s	7,50 dd	7,64 d	—	—	$J_{12}=2,9$; $J_{13}=1,7$; $J_{14}=0,8$; $J_{23}=2,7$; $J_{45}=8,6$
XII	H	6,90 dd	7,25 dd	11,0s	7,52[a] d	7,85[a] d	—	—	$J_{12}=3,0$; $J_{13}=2,0$; $J_{23}=2,6$; $J_{45}=9,0$

[a]Reverse assignments of the indicated signals are possible.
[b]With d_6-acetone as the solvent.

indole, 1H,6H-indolo[7,6-g]indole [9], indoloindole XI, and indoloindole XII (Fig. 2) shows that the absorption of the indoloindoles is similar in character to the absorption of indole but that the spectra of indoloindoles XI and XII are more structured and resemble the spectrum of the isomeric 1H,6H-indolo[7,6-g]indole with respect to the absorption maxima.

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254. The IR sepctra were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were obtained with a Specord spectrophotometer. The PMR spectra of III-X and XII were recorded with a Varian CFT-20 spectrometer with tetramethylsilane (TMS) as the internal standard; the PMR spectrum of XI was recorded with a WP-200 SY spectrometer with TMS as the internal standard. Preparative chromatography was carried out on SiO_2 (100-160 μm particles). The mass spectra were recorded with a R 10-10 NERMAG'S spectrometer.

The constants and yields of III-XII are presented in Table 3. The 2,7- and 2,6-naphthylenedihydrazines were obtained by the method in [3].

2,7-Naphthylenedihydrazine Dihydrochloride (I). A 10-g sample of 2,7-naphthylenedihydrazine was added in small portions with stirring to 220 ml of concentrated HCl, and the mixture was refluxed for 1 h. It was then cooled, and the solid product was removed by filtration, washed successively with isopropyl alcohol and ether, and dried over $CaCl_2$ to give a white

TABLE 3. Constants and Yields of the Synthesized Compounds

Compound	mp, °C	R_f	IR spectrum,[a] cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Found C, %	Found H, %	Found N, %	Found M+	Empirical formula	Calc. % C, %	Calc. % H, %	Calc. % N, %	Calc. % M	Yield, %
III	195—196		3400, 3275, 1720—1760		58,3	4,9	17,4		$C_{16}H_{16}N_4O_4$	58,6	4,9	17,1		96
IV	190—191		3400, 3305, 3310, 1730, 1710		58,8	5,0	17,3		$C_{16}H_{16}N_4O_4$	58,6	4,9	17,1		67
Va	141—142	0,65 benzene—hexane, 5:2)	3285, 1690	203 (4,36), 218 (4,33), 256 (4,34), 321 sh (4,22), 370 (4,57)	62,2	6,1	14,2		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		8
Vb	139—140	0,76 benzene—ether, 1:1)	3280, 3370, 1690—1720	212 (4,37), 252 (4,37), 316 sh (4,41), 357 (4,62)	62,6	6,4	14,4		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		12
Vc	186—187	0,42 benzene—ether, 1:1)	3370, 1720	210 (4,42), 248 (4,40), 312 (4,49), 344 (4,73)	62,3	6,2	14,5		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		60
VIa	198—199	0,6 benzene	3270, 1680	238 (4,02), 263 sh (3,89), 294 (3,67), 406 (4,22)	62,2	6,3	14,9		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		4
VIb	127—128	0,71 benzene—ether, 1:1)	3220—3300, 1690, 1610	236 (4,52), 291 (4,28), 395 (4,57)	62,3	6,0	14,2		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		14
VIc	201—202	0,31 benzene—ether 1:1)	3330, 1695	243 (4,39), 292 (4,26), 375 (4,55)	62,4	6,6	14,3		$C_{20}H_{24}N_4O_4$	62,5	6,3	14,6		25
VII	315—316	0,75 benzene—acetone, 2:1)	3330, 1680—1710	202 (4,07), 236 (4,20), 280 sh (3,98), 293 sh (4,22), 303 (4,36), 322 (3,87), 335 sh (3,70), 353 (3,77), 370 (3,82)	68,8	5,4	8,2	350	$C_{20}H_{18}N_2O_4$	68,6	5,1	8,0	350	38
VIII	322	0,62 benzene—ether, 1:1)	3285, 3340, 1680	253 (4,58), 262 sh (4,42), 270 (4,32), 279 (4,31), 288 (4,26), 338 (4,36), 354 (4,39), 372 (4,39)	68,8	5,4	8,1	350	$C_{20}H_{18}N_2O_4$	68,6	5,1	8,0	350	38
IX	220 (dec.)	0,49 benzene—acetone, 1:1)	3430, 3300—3330, 1700	236 (4,56), 278 sh (4,36), 289 sh (4,60), 298 (4,75), 315 sh (4,27), 333 sh (4,04), 350 (4,05)	65,2	3,3	9,7		$C_{16}H_{10}N_2O_4$	65,3	3,4	9,5		66
X	250 (dec.)	0,6 benzene—acetone, 1:2)	4330, 4400, 3350, 1700	238 (3,34), 253 (3,14), 269 (3,00), 321 (2,71), 333 (2,88), 351 (2,87), 368 (2,91)	65,2	3,4	9,5		$C_{16}H_{10}N_2O_4$	65,3	3,4	9,5		63
XI	260 (dec.)	0,46 benzene—acetone, 4:1)	3400—3420	201 (4,40), 232 (4,38), 253 sh (4,38), 262 (4,70), 271 (4,85), 301 (3,99), 309 (3,88), 323 (3,34)	81,5	5,0	13,7	206	$C_{14}H_{10}N_2$	81,6	4,9	13,6	206	28
XII	268—269	0,52 benzene—ether, 5:1)	3400, 3360	204 (4,53), 215 (4,61), 244 (4,62), 257 sh (4,33), 302 (4,02), 317 (4,23), 326 sh (4,10), 333 (4,10), 341 (3,96), 348 (3,98)	81,8	5,3	13,6	206	$C_{14}H_{10}N_2$	81,6	4,9	13,6	206	6

[a]The spectra of V and VI were recorded from solutions in chloroform, whereas the spectra of the remaining compounds were recorded from suspensions in mineral oil.

powder in quantitative yield. The product decomposed above 300°C. Found: C 45.3; H 5.8; Cl 27.4; N 21.0%. $C_{10}H_{12}N_4 \cdot 2HCl$. Calculated: C 45.8; H 5.4; Cl 27.2; N 21.5%.

2,6-Naphthylenedihydrazine Dihydrochloride (II). This compound was similarly obtained in quantitative yield at room temperature. The product decomposed at 290°C. Found: C 45.3; H 5.7; Cl 27.6; N 21.5%. $C_{10}H_{12}N_4 \cdot 2HCl$. Calculated: C 45.8; H 5.4; Cl 27.2; N 21.5%.

Pyruvic Acid 2,7-Naphthylenedihydrazone (III). An aqueous solution of I obtained from 9.4 g (0.05 mole) of the dihydrazine was added in a fine stream to an aqueous solution of 10.9 ml (0.15 mole) of freshly distilled pyruvic acid, and the mixture was stirred for 1 h. The precipitate was removed by filtration, washed with water, and dried. The substance was washed with ethanol for analysis.

Pyruvic acid 2,6-naphthylenedihydrazone (IV) was similarly obtained.

Ethyl Pyruvate 2,7-Naphthylenedihydrazone (V). An aqueous solution of I obtained from 2.8 g (0.015 mole) of 2,7-naphthylenedihydrazine was treated with sodium acetate to pH 4, and the mixture was added in a fine stream with stirring to a solution of 4.9 ml (0.045 mole) of ethyl pyruvate in 5 ml of ethanol. The mixture was then stirred for 1 h, and the resulting precipitate was removed by filtration and dried to give 3.9 g (68%) of product. Separation of the mixture of isomers into individual isomers was carried out with a column; isomer Va was eluted with benzene, and isomers Vb and Vc were eluted with benzene–ether (5:1).

Ethyl pyruvate 2,6-naphthylenedihydrazone (VI) was similarly obtained; isomer VIa was eluted with benzene, and isomers VIb, c were eluted with benzene–ether (3:1).

2,9-Diethoxycarbonyl-3H,8H-indolo[4,5-e]indole (VII). A 15-g sample of ethyl polyphosphate (EPP) was added to 1 g (0.003 mole) of V, and the mixture was heated to 70°C and stirred for 20 min. The mixture was treated with water at room temperature, and the precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 0.86 g (95%) of product. The product was purified with a column by elution with benzene to give 0.33 g (38%) of analytically pure VII.

2,7-Diethoxycarbonyl-3H,8H-indolo[5,4-e]indole (VIII) was similarly obtained at 75-78°C and was purified by elution with chloroform.

2,9-Dicarboxy-3H,8H-indolo[4,5-e]indole (IX). A 6.56-g (0.02 mole) sample of dihydrazone III was suspended in 300 ml of glacial acetic acid, the suspension was heated at 70°C, 15 ml of concentrated H_2SO_4 was added, and the mixture was stirred at 70-75°C for 10 min. It was then poured into cold water, and the precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 3.9 g (66%) of product. For analysis, IX was obtained by saponification of pure VII.

2,7-Dicarboxy-3H,8H-indolo[5,4-e]indole (X) was similarly obtained at 80°C.

3H,8H-Indolo[4,5-e]indole (XI). A 1.4-g (6.7 mmole) sample of IX was placed in a flask equipped with a gas outlet tube and heated at 200°C for 10-15 min until CO_2 evolution ceased. The reaction mass was then cooled to room temperature and extracted with acetone. The extract was evaporated, and the product was dried and chromatographed with a column by elution with benzene to give colorless shiny crystals, which gave a blue coloration with Erlich's reagent at room temperature.

3H,8H-Indolo[5,4-e]indole (XII) was similarly obtained at 270°C.

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ELECTROCHEMICAL SYNTHESIS OF 2,2,6,6-TETRAMETHYLPIPERIDINE

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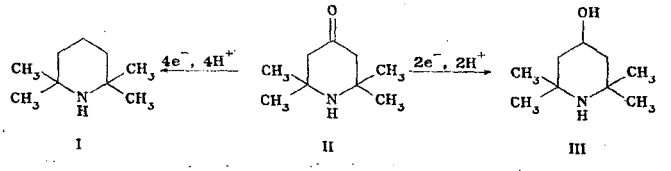
A preparative method for the production of 2,2,6,6-tetramethylpiperidine based on the electrochemical reduction of 4-oxo-2,2,6,6-tetramethylpiperidine in 30% sulfuric acid on cadmium or lead electrodes was developed.

2,2,6,6-Tetramethylpiperidine (I) is used for the synthesis of the medicinal preparation pempidine [1] and the corresponding nitroxyl radical, which is widely used as a spin probe [2], for the stabilization of polymers [3, 4], and for the inhibition of radical polymerization [4, 5].

The known method for the preparation of 2,2,6,6-tetramethylpiperidine (I), which is based on the reduction of 4-oxo-2,2-6,6-tetramethylpiperidine (II) (triacetonamine) with hydrazine, is rather complex, and this limits its use [1].

We have established that two compounds viz, 2,2,6,6-tetramethylpiperidine (I) and 4-hydroxy-2,2,6,6-tetramethylpiperidine (III), are simultaneously formed in the electrochemical reduction of triacetoneamine in an acidic medium on cathodes with high hydrogen overvoltages (cadmium and lead):



Compound III is an important intermediate in the synthesis of stabilizers for polymeric materials [4, 6].

The ratio of the products of electrochemical reduction of triacetonamine concentration stantially on its concentration and the amount of free sulfuric acid in the electrolyte. When the electrolysis is carried out in 30% sulfuric acid at a triacetonamine concentration of 0.65 mole/liter, the yield of 2,2,6,6-tetramethylpiperidine (I) exceeds 65%, and the yield of 4-hydroxy-2,2,6,6-tetramethylpiperidine (III) is 20%. When the triacetonamine concentration is increased to 1.3 moles/liter, the yield of alcohol III increases to 25-27%, and the yield of 2,2,6,6-tetramethylpiperidine (I) decreases correspondingly.

Alcohol III was obtained in virtually quantitative yield by the electrochemical reduction of triacetonamine in an alkaline medium (4% sodium hydroxide solution at a triacetonamine concentration of 0.25 mole/liter [7].

No substantial effect on the yields of the reaction products was observed when the temperature was varied from 25 to 65°C and the current density was varied from 0.05 to 0.01 A/cm^2.

The separation of I and III does not present any difficulties and can be achieved by removal of I from nonvolatile alcohol III by distillation.

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