INDOLES

XX.* SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF

2,3,3a,8a-TETRAHYDROFURO[2,3-b]INDOLE

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N-Substituted derivatives of 3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole were synthesized by the reaction of α -substituted arylhydrazine salts with 3-methylpentan-4-on-1-ol by heating the components in dimethylformamide.

In continuing our investigations associated with the synthesis of structural analogs of physovenine [2-4], we have succeeded in obtaining N-substituted derivatives of 3a,8a-dimethyl-2,3a,8a-tetrahydrofuro-[2,3-b]indole (III-VIII).

The reaction occurs by heating α -substituted arylhydrazines with 3-methylpentan-4-on-1-ol in dimethylformamide via the standard Fischer scheme [2, 3]:



VIII $R = OCH_3$, $R' = CH_3$

It follows from this scheme that substituent R' should, in all likelihood, have had a definite effect on the ease of occurrence of the individual steps of the reaction, particularly on the ease of formation of intermediate product II from I and III-VIII from IIa. However, in the majority of cases this could not be noted. Almost all of the substituted hydrazines cyclized with the same ease to tetrahydrofuroindoles (Tables 1 and 2). α, α -Diphenylhydrazine (VI) constituted an exception. In this case the decrease in the basicity of the nitrogen atom led to a sharp drop in the yield under standard conditions, and only an increase in the heating time to 3 h (instead of 15 min) raised the yield to 76%. The pronounced decrease in the basicity of the nitrogen atom in the case R' = C₆H₅ also explains the impossibility of obtaining a picrate for VI. Steric factors probably play a definite role in this case.

*See [1] for communication XIX.

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Com- pound	bp (mm)	mp	UV spectr.		Rt				Found,		Calc.,		ł
			λ _{max} , nm	lge	Al ₂ O ₃		р р	Empirical	%		%		
					hexane -ether (4:1)	CHCi3	acetylate	formula	с	н	с	н	Yield, %
III	119—122 (2)	- <u></u> -	250 300	3,95 3,40	0,41	0,84	0,44	C ₁₃ H ₁₇ NO	77,0	8,5	76,8	8,4	92
IV	135—138 (8)	25—26	255 307	4,08 3,65	0,50	0,82	0,41	C ₁₅ H ₂₁ NO	77,9	9,4	77,9	9,2	73
V	165—170 (2)		250 302	4,08 3,47	0,35	0,83	0,49	C ₁₉ H ₂₁ NO	81,4	7,8	81,7	7,6	55
VI	183—186 (3)	—	245 281	3,99 3,18	0,45	0,86	0,50	C ₁₈ H ₁₉ NO	81,2	7,2	81,5	7,2	76
VII	115—117 (1)		250 308	4,11 3,49	0,43	0,81	0,64	C14H19NO	77,2	8,8	77,4	8,8	78
VIII	121—124 (2)		248 319	3,90 3,46	0,23	0,71	0,52	C ₁₄ H ₁₉ NO ₂	72,2	8,1	72,1	8,2	51

TABLE 1. Characteristics of the Tetrahydrofuro[2,3-b]indole Derivatives

* Before chromatographic purification.

TABLE 2. Picrates of the Tetrahydrofuro[2,3-b]indole Derivatives

Com-			N, %			
pound	mp (from alcohol)	Empirical formula	found	calc.		
III IV V VII VIII	$117-118,5 \\ 114-115,5 \\ 174,5-175,5 \\ 167-168 \\ 161,5-162$	$\begin{array}{c} C_{13}H_{17}NO \cdot C_6H_8N_3O_7\\ C_{16}H_{21}NO \cdot C_6H_3N_3O_7\\ C_{19}H_{21}NO \cdot C_6H_3N_3O_7\\ C_{14}H_{19}NO \cdot C_6H_3N_3O_7\\ C_{14}H_{19}NO \cdot C_6H_3N_3O_7\\ C_{14}H_{19}NO_2 \cdot C_6H_3N_3O_7\\ \end{array}$	13,1 12,0 11,2 12,8 12,5	13,0 12,2 11,0 12,5 12,1		

EXPERIMENTAL

Commercial α -methyl- α -phenyl-, α -benzyl- α -phenyl-, and α , α -diphenylhydrazine hydrochlorides were used without additional purification.

<u> α -Isopropyl- α -phenylhydrazine</u>. A solution of 75.2 g (0.56 mole) of N-isopropylaniline in 570 ml of 2 N sulfuric acid was nitrosated with 38.4 g of sodium nitrite in 110 ml of water at 0-2°. The mixture was extracted with ether, the extract was dried with CaCl₂, the ether was removed by distillation, and the residue was vacuum distilled to give 68.5 g (75%) of N-nitroso-N-isopropylaniline with bp 134-135° (14 mm) and n_D^{14} 1.5370. A solution of 24.6 g (0.15 mole) of the N-nitroso derivative in 120 ml of absolute ether was treated with stirring with a suspension of 8 g of lithium aluminum hydride in 250 ml of absolute ether, holding the reaction mass at the boiling point, after which it was refluxed for 1 h and stirred at room temperature for another 2 h. It was then allowed to stand overnight, 50 ml of moist ether was added, and water was added dropwise until a gelatinous mass was obtained. Aqueous alkali was then added until a white, amorphous precipitate formed. The mixture was allowed to stand for 1 h, filtered, and the precipitate on the filter was washed with ether. The filtrate was dried with KOH, the ether was removed by distillation, and the residue was vacuum distilled to give 20.5 g (91%) of α -isopropyl- α -phenylhydrazine with bp 98-102° (3 mm) and n_D^{20} 1.5539. The hydrochloride had mp 150-151.5° (from ethanol with ether) [5].

The following two arylhydrazines were obtained under similar conditions.

 α -Methyl- α -(p-tolyl)hydrazine. N-Nitroso-N-methyl-p-toluidine was synthesized from N-methyl-p-toluidine and had mp 51-52.5° (from ethanol-ether). α -Methyl- α -(p-tolyl)hydrazine was obtained in 68% yield from the N-nitroso derivative and had bp 119-121° (14 mm). The hydrochloride had mp 146-148° (from ethanol-ether) [6].

 α -Methyl- α -(p-anisyl)hydrazine. N-Nitroso-N-methyl-p-anisidine was synthesized from N-methyl-p-anisidine and had mp 42-43° (from ethanol-ether). α -Methyl- α -(p-anisyl)hydrazine was obtained in 63%

yield from the N-nitroso derivative and had bp 120-123° (5 mm). The hydrochloride had mp 142-144° (from ethanol-ether) [7].

<u>General Method for the Preparation and Purification of 2,3,3a,8a-Tetrahydrofuro[2,3-b]indole Derivatives.</u> A mixture of 0.05 mole of arylhydrazine hydrochloride and 0.05 mole of 3-methylpentan-4-on-1-ol [3] in 50 ml of dimethylformamide was heated at 50° for 30 min, for 30 min on a boiling-water bath, and refluxed for another 15 min.* The dimethylformamide was vacuum distilled from the reaction mixture, 50 ml of water was added to the residue, and the mixture was extracted with benzene. The benzene extract was evaporated, and the residue was vacuum distilled. The crude product obtained was additionally purified by means of adsorption chromatography as follows. A total of 2 g of the substance obtained after distillation was passed through a 55-cm long column 2 cm in diameter filled with activity II aluminum oxide using hexane -ether (4:1) as the eluent,† An analytically pure sample (1,2-1.5 g) was obtained from the eluate.

The degree of purity of the compound was monitored on a loose layer of activity II aluminum oxide (layer thickness 0.6-0.7 mm) in a hexane-ether (4:1) system and in chloroform. The chromatograms were developed with iodine vapors. Paper chromatography was carried out on acetylated paper with chloroform as the stationary phase and 80% ethanol as the mobile phase [3, 8]. The chromatograms were developed with an alcohol solution of ninhydrin with prior exposure of the chromatograms in a chamber filled with iodine vapors.

The UV spectra of 80% ethanol solutions were obtained with an EPS-3T spectrometer.

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^{*} The reflux time was increased to 3 h for VI.

 $[\]dagger$ Hexane-ether (9:1) was used as the eluent for VI.