

INDOLES

XXIII.* SYNTHESIS OF 3a,8a-DISUBSTITUTED DERIVATIVES OF
2,3,3a,8a-TETRAHYDROFURO[2,3-b]INDOLE

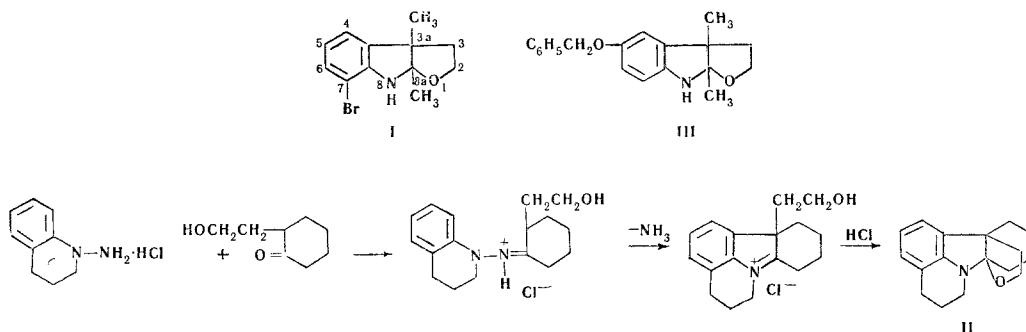
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Tetrahydrofuro[2,3-b]indole derivatives are formed by refluxing arylhydrazine salts in alcohol with γ -hydroxy ketones that have an α -methylidyne group.

The possibility of the synthesis of tetrahydrofuro[2,3-b]indole derivatives by heating arylhydrazine salts with 3-methylpentan-4-on-1-ol in dimethylformamide was investigated in [2,3]. However, subsequent investigations showed that performing the reaction under these conditions does not always lead to the desired result. In particular, the reaction of *o*-bromophenylhydrazine hydrochloride with 3-methylpentan-4-on-1-ol gives, instead of the expected I, N-formyl-*N'*-(*o*-bromophenyl)hydrazine as a consequence of formylation of the starting hydrazine by the solvent.

When we used isopropyl alcohol as the solvent, we were able to accomplish the reaction of *o*-bromo-phenylhydrazine hydrochloride with 3-methylpentan-4-on-1-ol and isolated 7-bromo-3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole (I).



The reaction proved to be convenient for the preparation of more complex compounds of this type, for example, II and 5-benzyloxy-3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole (III), unsuccessful attempts to synthesize which have already been mentioned in [4].

We were unable to obtain tetrahydrofuro[2,3-b]indole derivatives by using arylhydrazines with strong electron-acceptor substituents in the benzene ring. Thus only *p*-nitroaniline could be isolated as one of the products of the decomposition of *p*-nitrophenylhydrazine when *p*-nitrophenylhydrazine hydrochloride was refluxed with 3-methylpentan-4-on-1-ol in dimethylformamide or isopropyl alcohol for 20 h.

To synthesize tetrahydrofuro[2,3-b]indole derivatives with various substituents attached to the 3a- and 8a carbon atoms, it was necessary to obtain the appropriate γ -hydroxy ketones; this was accomplished via the scheme shown on page 730.

Acylation of butyrolactone by the ethyl ester of the appropriate acid under the conditions of the Claisen reaction gave IV-VI, the sodium derivatives of which were then alkylated with a suitable alkyl halide (iodides were best) in dimethyl sulfoxide (VIIa-d) (Table 1).

*See [1] for communication XXII.

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TABLE 1. Characteristics of the α -Alkyl- α -acylbutyrolactones

Comp.	Bp, °C (press., mm)	Mp, °C (benzene- hexane)	d_{4}^{20}	n_{D}^{20}	UV spectrum*		IR spectrum, cm $^{-1}$	GLC reten- tion time, min †	Empirical formula	Found, %		Calc., %		Yield, %
					λ_{max}^{max} nm	lg e				C	H	C	H	
VIIa	126—127 (10)	—	1,1004	1,4588	220 280 252 258 264 286**	2,45 2,27 2,20 2,40 2,36 1,98	1710 1765 1720 1756	10,5	C ₉ H ₁₄ O ₃	63,2	8,3	63,5	8,3	81
VIIb	138—142 (1)	48— —49,5	—	—	252 258 264 286**	2,20 2,40 2,36 1,98	105,5	—	C ₁₃ H ₁₄ O ₃	71,4	6,6	71,5	6,5	89
VIIc	92—93 (1)	—	1,1097	1,4572	2134*	2,29 2,84 1,67	1715 1770	11	C ₉ H ₁₄ O ₃	63,5	8,3	63,5	8,3	85,5
VIIId	137—140 (0,5)	26— —27,5	—	—	252 257 289	2,82 2,81 2,04	1720 1773	151	C ₁₃ H ₁₄ O ₃	71,2	6,6	71,5	6,5	76,4

* In ethanol.

† Valence vibrations of the acyl and lactone carbonyl groups, respectively.

‡ Obtained using a Tsvet-1 chromatograph with a flame-ionization detector and a 2-m long column packed with Chromosorb G (45–60 mesh) with 6% polyethylene glycol succinate. The column temperature was 176°, the vaporizer temperature was 215°, and the gas-carrier (nitrogen) flow rate was 45 ml/min.

** Inflection.

TABLE 2. Characteristics of the γ -Hydroxy Ketones

Compound	Bp, °C (press., mm)*	IR spectrum, $\nu_{C=O}$, cm $^{-1}$	GLC retention time, min †	Yield, %‡
3-Methylpentan-4-on-4-ol	55—58 (1)	1710	1,5	70
VIII a	57—60 (10)	1710	2,1	73
VIII b	91—94 (1)	1705	19,9	71
VIII c	44—48 (8)	1705	1,9	75
VIII d	112—116 (1)	1670	—	78

* Of the analyzed fraction.

† Obtained using a Tsvet-1 chromatograph with a flame ionization detector and a 2-m long column packed with Chromosorb G (45–60 mesh) with 6% polyethylene glycol succinate. The column temperature was 178°, the vaporizer temperature was 237°, and the gas carrier (nitrogen) flow rate was 15 ml/min.

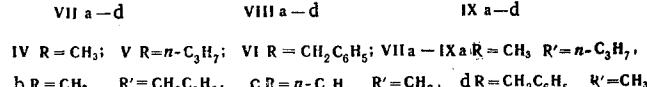
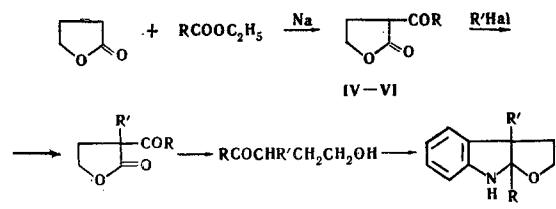
‡ Based on the γ -hydroxy ketone.

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

Comp.	Bp, °C (press., mm)	Mp, °C	UV spectrum		R _f			Empirical formula	Found, %		Calc., %		Yield, %		
					Al ₂ O ₃										
			λ_{max} nm	lg ε	benzene- isopropanol (9:1)	CHCl ₃	CHCl ₃		C	H	C	H			
I	125—131 (1,5)	98—99	234 243 299 253	3,81 3,84 3,50 4,28	0,66 0,62 0,11	0,62 — 0,60	0,38 — —	C ₁₂ H ₁₄ BrNO	53,7 80,0 76,9 C ₁₇ H ₂₁ NO	5,3 8,5 7,2 80,0	53,8 8,3 77,3 8,3	5,3 62	67		
II	142—146 (1)	—	302 271	3,75 3,95	0,55	0,11	—	C ₁₉ H ₂₁ NO ₂ ^b	77,5 81,2 77,2	8,9 7,3 8,7	77,4 81,5 77,4	8,8 7,2 8,8	53		
III	216—221 (1,5)	71,5—72,5	217 ^c 223 250 247	4,26 4,10 3,79 3,70	0,50	0,11	0,80	C ₁₄ H ₁₉ NO ^d	77,5 81,2 77,2	8,9 7,3 8,7	77,4 81,5 77,4	8,8 7,2 68	42		
IX a	163—165 (4)	74—75,5	217 ^c 223 250 247	4,26 4,10 3,79 3,70	0,50	0,11	0,80	C ₁₈ H ₁₉ NO ^e	77,5 81,2 77,2	8,9 7,3 8,7	77,4 81,5 77,4	8,8 7,2 65			
IX b	208—214 (1,5)	123,5— —124,5	216 ^c 223 247	4,13 3,98 3,76	0,59	0,31	0,70	C ₁₄ H ₁₉ NO	77,5 81,2 77,2	8,9 7,3 8,7	77,4 81,5 77,4	8,8 7,2 68			
IX c	137—141 (2)	63,5—64,5	216 ^c 223 247	4,13 3,98 3,76	0,59	0,31	0,70	C ₁₈ H ₁₉ NO ^e	77,5 81,2 77,2	8,9 7,3 8,7	77,4 81,5 77,4	8,8 7,2 68			
IX d	173—178 (1,5)	61—62	225 ^c 243	3,93 3,86	0,68	0,57	0,49	C ₁₈ H ₁₉ NO	81,8 81,8	7,4 7,4	81,5 81,5	7,2 7,2	81		

^aIn 80% ethanol.

^bPicrate, mp 163—164° (from alcohol). Found %: N 10.7.

C₁₉H₂₁NO₂ · C₆H₃N₃O₇. Calculated %: N 10.7.

^cInflection.

^dPicrate, mp 136—137° (from alcohol). Found %: N 12.7.

C₁₄H₁₉NO · C₆H₃N₃O₇. Calculated %: N 12.6.

^ePicrate, mp 105—107°. Found %: N 11.7. C₁₈H₁₉NO · C₆H₃N₃O₇.

Calculated %: N 11.3.

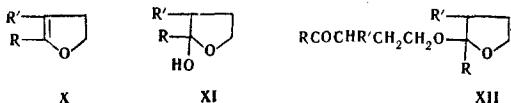
The hydrolysis of the α -alkyl- α -acylbutyrolactones by refluxing in 5% hydrochloric acid should have given the corresponding γ -hydroxy ketones (VIIIa-d). However, the latter could not be isolated as pure compounds with sharp boiling points. The data of elementary analysis demonstrated that the percentage of carbon and hydrogen for the γ -hydroxy ketones were too high as compared with the calculated values. Their PMR spectra in CC₄ indicate a mixture of at least two compounds, which does not make it possible to make a clear assignment of the proton signals. The difficulties arising during the mass-spectral investigation of hydrolysis products VIIIa-d (poor reproducibility of the spectra and the absence of a molecular ion) also made it impossible to ascertain their compositions.

At the same time, gas-liquid chromatography characterizes them as pure compounds — dihydrofuran derivatives (X). This assertion is based on the fact that γ -acetylpropanol and its dehydration product — 2-methyl-4,5-dihydrofuran (X, R = CH₃, R' = H) — have the same retention time, while the retention times of other γ -hydroxy ketones (except aryl-substituted ones) are of the same order of magnitude (see Table 2).

The IR spectra of the γ -hydroxy ketones contained an absorption band at 1710 cm⁻¹ corresponding to the valence vibration of the carbonyl group with an intensity somewhat lower than the literature values [5] (for γ -acetylpropanol the integral intensity of the carbonyl band is A = 5.8 · 10³ liter/mole-cm², while A = 5.2 · 10³ liter/mole-cm² for 3-methylpentan-4-on-1-ol).

These anomalies in the behavior of γ -hydroxy ketones that have an α -methylidyne group can be explained as follows. The substance obtained by the hydrolysis of α -alkyl- α -acylbutyrolactone with subsequent distillation is in all likelihood a mixture of γ -hydroxy ketone (VIIIa-d), its hemiacetal (XI) (there are indications that γ -acetylpropanol is an allelotropic mixture of the open and hemiacetal forms with predominance of the former [6, 7]), and dehydration products. The latter include dihydrofuran X and possibly the labile product of the addition of the γ -hydroxy ketone to the dihydrofuran (XII).

The presence of dehydration products may explain the elevated results of elementary analysis. The assumption of the lability of XII follows from the results of the determination of the molecular weight of 3-



methylpentan-4-on-1-ol by isothermal distillation in CCl_4 . The molecular weight thus obtained indicates the presence in solution of only monomers (the hydroxy ketone and, probably, 2,3-dimethyl-4,5-dihydrofuran).

It should be noted that the possibility of interconversions between these forms as a result of the interaction of various factors (temperature, solvent) as well as the predominance of any one of them as a function of the substituent are not excluded.

Nevertheless, this mixture does successfully react with arylhydrazine hydrochlorides to give compounds with the three-ringed structural base of physovenine (Table 3), since all forms react in the same way in this reaction. (See [8] for the reaction of arylhydrazine salts with dihydropyrans.)

EXPERIMENTAL

The degree of purity of the compounds was monitored on a loose layer of activity II aluminum oxide (layer thickness 0.6–0.7 mm) in benzene–isopropyl alcohol (9:1) and in chloroform. The chromatograms were developed with iodine vapors. Paper chromatography was carried out on acetylated paper using chloroform as the stationary phase and 80% ethanol as the mobile phase [2,3]. The chromatograms were developed with an alcohol solution of ninhydrin with prior storage of the chromatograms in a chamber filled with iodine vapors.

The UV spectra of ethanol solutions were recorded with an EPS-3T spectrometer. The IR spectra in thin layers or potassium bromide pellets of the lactones and γ -hydroxy ketones were recorded with a Jasco-IRS spectrometer with a NaCl prism.

α -Butyrylbutyrolactone (V). With stirring, 118 g (1.02 mole) of ethyl butyrate and 23.8 g (1.03 g-atom) of sodium in small portions were added in the course of 7 h to 86 g (1 mole) of butyrolactone at 105–115°; after this, another 35.5 g (0.303 mole) of ethyl butyrate was added. The reaction mass was then held at the same temperature for 1 h, cooled to 75°, and treated with 150 ml of 50% acetic acid. The organic layer was washed with 270 ml of saturated sodium chloride solution, and the aqueous phase was extracted with ether. The ether extract was combined with the organic layer, washed with 50 ml of 5% sodium bicarbonate and 35 ml of water, and dried with magnesium sulfate. The residue after removal of the ether by distillation was vacuum distilled to give 57.5 g (37%) of α -butyrylbutyrolactone with bp 103–105° (0.5 mm), d_4^{20} 1.1233, and n_D^{20} 1.4594. Found %: C 61.6; H 7.9. $\text{C}_8\text{H}_{12}\text{O}_3$. Calculated %: C 61.5; H 7.7. UV spectrum: λ_{max} 256 nm ($\log \epsilon$ 2.98). IR spectrum: $\nu_{\text{C=O}}$ 1726, 1770 cm^{-1} .

α -Phenylacetylbutyrolactone (VI). This was obtained in 66% yield under similar conditions from butyrolactone and ethyl phenylacetate and had bp 170–180° (2.5 mm) and mp 42–43.5° (benzene–hexane). Found %: C 70.7; H 6.0. $\text{C}_{12}\text{H}_{12}\text{O}_3$. Calculated %: C 70.6; H 5.9. UV spectrum, λ_{max} , nm ($\log \epsilon$): 258 (3.38), 254 (3.36) (inflection), 263 (3.34). IR spectrum: $\nu_{\text{C=O}}$ 1720, 1758 cm^{-1} .

α -Alkyl- α -acylbutyrolactones (VIIa–d). A total of 0.3 mole of α -acylbutyrolactone was added with stirring to a solution of 6.9 g (0.3 g-atom) of sodium in 75 ml of absolute alcohol. After 30 min, 60 ml of dimethyl sulfoxide was added, and the alcohol was removed by vacuum distillation. A total of 0.45 mole of alkyl halide was added slowly with stirring to the resulting solution (the reaction was strongly exothermic), and the reaction mass was heated at 50° for 1 h, after which 300 ml of absolute benzene was added and the mixture was filtered. The precipitate on the filter was washed thoroughly with absolute benzene, dissolved in 90 ml of water, and extracted with benzene. All of the benzene fractions were combined, the benzene was evaporated, and the residue was vacuum distilled.

Hydrolysis of α -Alkyl- α -acylbutyrolactones VIIa–d. A mixture of 0.15 mole of lactone VII and 200 ml of 5% hydrochloric acid was refluxed for 5 h, cooled, and saturated with solid potassium carbonate. The mixture was extracted with ether, and the ether extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was vacuum distilled.

2,3,3a,8a-Tetrahydrofuro[2,3-b]indole Derivatives (I–III, IXa–d). A mixture of 0.05 mole of the arylhydrazine hydrochloride and 0.05 mole of the γ -hydroxy ketone was refluxed in 100 ml of isopropyl alcohol

for 5 h. The alcohol was distilled from the reaction mass, and the residue was treated with 50 ml of water and extracted with benzene. The benzene extract was evaporated, and the residual viscous oil was vacuum distilled and recrystallized from hexane.

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