BENZINDOLES

XI.* 3-FORMYL[4,5]- AND 3-FORMYL[6,7]BENZINDOLES IN CROTONIC CONDENSATION WITH ACETONE

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UDC 547.759.31:542.955

Crotonic condensation of 3-formyl[4,5]- and 3-formyl[6,7]benzindoles with acetone on aluminum oxide or methylation of them with dimethyl sulfate in aqueous acetone solution in the presence of KOH gave [4, 5]- and [6,7]benzoskatolideneacetones. A number of 3-formylbenzindoles with various substituents in the pyrrole portion of the molecule are described.

It is well known that the reactivity of 3-formylindole in condensation reactions is determined by conjugation of the carbonyl group with the nitrogen atom of the pyrrole ring [2, 3]. The catalyst employed in the condensation and the alkalinity or acidity of the medium play an important role in this process. In addition, the products of condensation of 3-formylindole with ketones and aldehydes [4, 5] may be of interest as intermediates for the synthesis of diverse physiologically active indole derivatives. However, data on the use of 3-formyl[4,5]- and 3-formyl[6,7]benzindoles in crotonic condensation are unavailable.

As a rule [5], bases of the piperidine, methylamine, ammonium acetate, etc. type are used as catalysts for such reactions. On the other hand, the condensation of 3-formylindole by the action of aluminum oxide [6] and also during the Wittig reaction [6] has been described, and Orlova and co-workers explained this by means of the basic properties of the phosphorylid, which catalyzes the reaction of the enol form of 3-formylindole with acetone. A paper recently appeared [7] in which Semenov and co-workers carried out the crotonic condensation of 3-formylindole with acetone in alcohol under the influence of potassium hydroxide. We have found that severe conditions are unsuitable for the condensation of 3-formylbenzinoldes [8] with acetone: [4,5]benzoskatolideneacetone (I) is detected only by chromatography, and the yield of the [6,7]isomer (II) did not exceed 5-10%. We achieved better yields when we used aluminum oxide as the catalyst. The condensation with acetone proceeds readily at room temperature in the presence of alkali in the case of N-methyl-3-formyl[4,5]-and -[6,7]benzindoles. The methylation of the aldehydes can be carried out simultaneously with the crotonic condensation : by the action on these aldehydes of dimethylsulfate in aqueous acetone solution in the presence of KOH [9] we obtained N-methyl-4,5]- and -[6,7-benzoskatolideneacetones (III and IV) in quantitative yields (Table 1). Signals of vinyl protons at 6.6-7.8 ppm with a spin–spin coupling constant (SSCC) of 16 Hz, which is characteristic for their transoid orientation, are observed in the PMR spectra† of the benzoskatolideneacetones obtained. Absorption bands at 1600-1700 cm^{-1} related to the stretching vibrations of an exocyclic double bond (low-frequency band) and a carbonyl group (high-frequency band) appear in the IR spectra (Table 1). One's attention is drawn to the unusual distribution of the intensities of the bands of the double bond and carbonyl group, which, in all likelihood, is associated with the conformational peculiarities of the orientation of the diene system relative to the benzindole molecules. An investigation of the conformations of these compounds by IR, UV, and PMR spectroscopy is the subject of our next communication.

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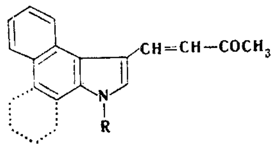
*See [1] for communication X.

†The PMR and UV spectral data will be given in our next communication.

D. I. Mendeleev Moscow Institute of Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1257-1261, September, 1975. Original article submitted November 19, 1974.

TABLE 1. [4,5]- and [6,7]Benzoskatolideneacetones



Compound	Fusion of the benzene ring	R	mp, °C[a]	Empirical formula	Found, %			IR spectrum, cm^{-1} (of crystals)
					C	H	N	
I	4,5	H	162	$C_{16}H_{13}NO$[b]	81,4	5,7	5,5	1570, 1610, 1672, 3170, 3190
II	6,7	H	206—207	$C_{16}H_{13}NO$[b]	81,4	6,4	5,8	1580, 1604, 1670, 3190, 3280
III	4,5	CH_3	157—158	$C_{17}H_{15}NO$[c]	81,6	6,1	5,4	1607, 1635, 1660
IV	6,7	CH_3	149	$C_{17}H_{15}NO$[c]	81,7	6,0	5,2	1590, 1620, 1665
V	Skatolideneacetone [7]		141—142					1565, 1590, 1662, 3196, 3470

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[a] These compounds were recrystallized from benzene–petroleum ether. [b] Calculated: C 81.6; H 5.6; N 5.9%. [c] Calculated: C 81.9; H 6.0; N 5.6%.

It is interesting to note that 2-methyl-3-formyl[6,7]benzindole reacts with dimethyl sulfate under similar conditions to give only an N-alkylation product – 1,2-dimethyl-3-formyl[6,7]benzindole.

3-Formylbenzindoles having substituents in the pyrrole portion of the molecule are presented in Table 2. The somewhat higher yields of the [6,7]derivatives may serve as an illustration of the previously drawn conclusion [10] that the electron density is higher on the $C_{(3)}$ atom in the [6,7]benzindole molecule.

EXPERIMENTAL

The PMR spectra were recorded with a Varian HA-100D spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra were obtained with a UR-10 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with a Shimadzu MPS-50L spectrophotometer.

N-Methyl[4,5]benzindole. A catalytic amount of ferric nitrate was added to a solution of 0.97 g of sodium in 150 ml of liquid ammonia, and, after 10 min, 4.5 g of [4,5]benzindole was added. The mixture was then stirred for 15 min, after which 2.6 g of methyl iodide was added dropwise, and the mixture was allowed to stand until the ammonia had evaporated completely. The residue was decomposed carefully by the addition of water, and the solid material was separated to give 4.3 g (88%) of a product with mp 40° (from petroleum ether). UV spectrum, λ_{max}, nm (log ε): 236 (4.50), 258 (4.54), 308 (3.90), and 320 (3.88). IR spectrum (CCl_4): no absorption in the region of NH vibrations, PMR spectrum in $(CD_3)_2SO$: $N-CH_3$ 3.73 (3H), 2-H 7.00 (1H) 3-H 6.92 (1H), $J_{2,3}=3.0$ Hz, 6-H 7.34 (1H), 7-H 7.74 ppm (1H), $J_{6,7}=8.5$ Hz. Found: C 86.5; H. 6.4; N 7.7%. $C_{13}H_{11}N$. Calculated: C 86.1; H 6.1; N 7.9%.

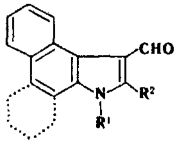
N-Methyl[6,7]benzindole. A similar reaction with 2.7 g of [6,7]benzindole, 1.6 ml of methyl iodide, and 0.54 g of sodium metal gave 2.2 g (75%) of N-methyl[6,7]benzindole with mp 65-66° (from petroleum ether). UV spectrum, λ_{max}, nm (log ε): 259 (4.70) and 281 (3.81). IR spectrum (in CCl_4): no absorption in the region of NH vibrations. PMR spectrum in $(CD_3)_2SO$, δ, ppm, J, Hz: $N-CH_3$ 4.22 (3H), 2-H 7.28 (1H), 3-H 6.50 (1H), $J_{2,3}=3.0$; 4-H 7.34 (1H), 5-H 7.74 (1H), $J_{4,5}=8.5$. Found: C 85.89; H 6.59; N 7.76%. $C_{13}H_{11}N$. Calculated: C 86.13; H 6.12; N 7.91%.

2-Methyl[4,5]benzindole. This compound, with mp 59-60° [bp 205-210° (10 mm) [12]], was obtained in 25% yield by the method in [11]. UV spectrum, λ_{max}, nm (log ε): 228 (4.54), 256 (4.52), 308 (3.88), and 324 (3.80). IR spectrum (in CCl_4): 3410 cm^{-1} (NH).

2-Methyl[6,7]benzindole. This compound, with mp 132° (from petroleum ether), was obtained in 53% yield by the method in [11]. UV spectrum, λ_{max}, nm (log ε): 220 (4.17), 246 (4.45), 264 (4.73), and 328 (3.18). IR spectrum (mineral oil): 3395 cm^{-1} (NH).

2-Phenyl[6,7]benzindole. This compound, with mp 166-167° (from benzene–petroleum ether), was obtained in 53% yield by the method in [13]. UV spectrum, λ_{max}, nm (log ε): 260 (4.30), 286 (4.56), 322 (4.32), and 354 (3.93). IR spectrum (mineral oil): 3445 cm^{-1} (NH).

TABLE 2. 3-Formyl[4,5]- and -[6,7]benzindoles



Fusion of the benzene ring	R¹	R²	mp, °C (solvent)	Empirical formula	Found, %			Calc., %			UV spectrum (in ethanol)		IR spectrum, cm⁻¹ (of crystals)	Yield, %
					C	H	N	C	H	N	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$		
4,5	H	H	196[8]										1650, 3200	86
4,5	CH_3	H	137 (benzene)	$C_{14}H_{11}NO$	80,7	6,4	6,8	80,4	5,3	6,7	218 252 274	34,6 15,8 25,2	1625, 1660	61
4,5	H	CH_3	285 (alcohol)	$C_{14}H_{11}NO$	80,6	5,4	6,2	80,4	5,3	6,7	244 250 282	17,3 14,2 24,5	1620, 1640, 3240	76
6,7	H	H	174—175[8]										1650, 3240	92
6,7	CH_3	H	159—160 (benzene)	$C_{14}H_{11}NO$	80,3	5,2	6,5	80,4	5,3	6,7	208 225sh 254 272	17,1 10,8 47,6 26,3	1660	80
6,7	H	CH_3	248—250 (alcohol)	$C_{14}H_{11}NO$	80,2	5,3	6,2	80,4	5,3	6,7	205 255 275	17,3 47,5 26,1	1630, 3200	88
6,7	H	C_6H_5	232—234 (aqueous alcohol)	$C_{19}H_{13}NO$	84,1	4,8	5,2	84,4	4,8	4,8	206 264 350sh	17,3 32,1 6,5	1630, 3320	61
6,7	CH_3	CH_3	149—150 (benzene)	$C_{15}H_{13}NO$	80,6	5,9	6,1	80,7	5,4	6,3	208 255 271 325	21,4 47,0 25,0 7,1	1650	Quant.

N-Methyl-3-formyl[4,5]benzindole. A) A solution of 0.75 g of N-methyl-[4,5]benzindole in 2 ml of dimethylformamide (DMF) was added dropwise at room temperature to the complex obtained by the usual method [8] from 0.5 ml of phosphorus oxychloride and 2 ml of DMF, after which the mixture was held at 35° for 40 min. The precipitated complex was then decomposed with water, and the mixture was heated with alkali solution. The mixture was then cooled, and the resulting crystals were separated, washed with water, and dried to give 0.53 g (61%) of a product with mp 137° (from benzene–petroleum ether). The other physical constants are presented in Table 2.

B) Dimethyl sulfate (2 ml) was added dropwise to a heated solution of 0.95 g of 3-formyl[4,5]benzindole [8] in 40 ml of ethanol and 80 ml of water containing 1.2 g of NaOH, after which heating was continued for another hour. The mixture was then cooled, and the resulting precipitate was separated to give 0.48 g (40%) of a product with mp 130-131°, which was chromatographically identical to a sample obtained by method A.

The isomeric 3-formylbenzindoles indicated in Table 2 were similarly obtained [8].

1,2-Dimethyl-3-formyl[6,7]benzindole. Dimethyl sulfate (1.2 ml) was added dropwise to a heated mixture of 0.4 g of 2-methyl-3-formyl[6,7]benzindole, 20 ml of acetone, 14 ml of water, and 1.4 g of KOH, after which the mixture was heated for another 20 min. The solvent was then removed by distillation, and the residue was separated to give a quantitative yield of the product. See Table 2 for the physical constants.

[4,5]Benzoskatolideneacetone (I). A total of 30 g of activity II aluminum oxide was added to a solution of 2 g of 3-formyl[4,5]benzindole in 35 ml of acetone, and the entire mass was allowed to stand at room temtemperature in a flask sealed with a glass stopper for 3 days. The solvent was then allowed to evaporate, and the dry mass was transferred to a column and eluted successively with petroleum and ether–petroleum ether (1:1); the yellow fraction was collected. The solvent was removed from the yellow fraction by distillation to give 0.73 g (62%) of I. The product was crystallized from benzene–petroleum ether to give yellow crystals with mp 162°. The results of elementary analysis and the UV and IR spectral data are presented in Table 1.

[6,7]Benzoskatolideneacetone (II). This compound was obtained under similar conditions from 1 g of 3-formyl[6,7]benzindole; the yield was 0.42 g (36%). The physical constants are presented in Table 1.

N-Methyl[4,5]benzoskatolideneacetone (III). A 1.6-g sample of dimethyl sulfate was added dropwise with heating to a solution of 0.7 g of 3-formyl[4,5]benzindole in 25 ml of acetone containing 1.4 g of KOH and 2.4 ml of water, after which stirring and heating were continued for another 20 min. The solvent was then removed by distillation, and the solid residue was separated, washed with water, and dried to give a quantitative yield of III (see Table 1).

N-Methyl[6,7]benzoskatolideneacetone (IV). A) A total of 0.57 g of IV (quantitative yield) was obtained from 0.5 g of 3-formyl[6,7]benzindole under the conditions presented above (see Table 1).

B) A solution of 1.4 g of KOH in 14 ml of water was added to a solution of 0.5 g of N-methyl-3-formyl[6,7]benzindole in 25 ml of acetone, and the mixture was stirred and heated for 20 min. The usual work workup gave 0.5 g of IV with mp 149°; no melting-point depression was observed for a mixture of this product with the sample described above, and the product was chromatographically identical to the latter.

LITERATURE CITED

1. T. K. Efimova, L. G. Tret'yakova, N. N. Suvorov, L. B. Shagalov, A. V. Karyakin, L. I. Anikina, V. M. Pivovarov, and T. A. Tkachenko, Khim. Geterotsikl. Soedin., 950 (1975).
2. V. P. Mamaev and L. S. Sandakchiev, Zh. Vsesoyuzn. Khim. Obshchestva, 3, 350 (1961).
3. N. N. Suvorov, I. A. Orlova, and K. F. Turchin, Khim. Geterotsikl. Soedin., 250 (1969).
4. R. C. Blume and H. G. Lindwall, J. Org. Chem., 11, 185 (1946).
5. S. V. Tsukerman, V. M. Nikitchenko, A. I. Bugai, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., 268 (1969).
6. I. A. Orlova, K. F. Turchin, and N. N. Suvorov, Zh. Organ. Khim., 7, 598 (1971).
7. A. A. Semenov, K. I. Kuchkova, and E. P. Styngach, Khim. Geterotsikl. Soedin., 1066 (1970).
8. L. B. Shagalov, T. A. Tkachenko, V. N. Eraksina, and N. N. Suvorov, Trudy MKhTI imeni D. I. Mendeleeva, 80, 65 (1974).
9. J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, St. Eardley, B. E. Jennings, and A. Robertson, J. Chem. Soc., 2227 (1957).

10. T. A. Babushkina, A. M. Vasil'ev, L. B. Shagalov, V. N. Eraksina, T. A. Tkachenko, and N. N. Suvorov, Zh. Organ. Khim., 11, 864 (1975).
11. A. Schlieper, Ann., 239, 229 (1887).
12. A. Reissert and J. Junghahn, Ber., 25, 2698 (1892).
13. H. P. Patel and J. M. Tedder, J. Chem. Soc., 4593 (1963).