

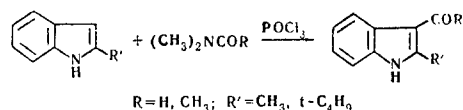
L. Kamenov,† L. G. Yudin,  
V. A. Budylin, and A. N. Kost

UDC 547.756.07:543.422.4

The synthesis of 2-substituted 3-acylindoles by various methods is described. It has been shown that branching both in the radical of the acyl group and in the substituent in position 2 creates hindrance for electrophilic attack.

The ortho effect, which has been well studied for six-membered aromatic compounds, does not always appear in five-membered, especially heterocyclic, structures since the distance between the substituents and the angles between the directions of the bonds differ from those in the corresponding benzoid systems. For example, electrophilic substitution in position 3 of indole-2-carboxylic acids encounters practically no steric hindrance as compared with unsubstituted indole [1]. At the same time, the carbonyl groups in 3-acylindoles have been found to show anomalous behavior, and when there is a substituent in position 2 they do not readily take part in the ordinary reactions of ketones [2]. Their IR spectra have considerable absorption at the frequency of the carbonyl group [3, 4]. Spectroscopic results indicate the presence of strong conjugation of the carbonyl group with the indole nucleus, although when a neighboring substituent is present it is possible to consider that the carbonyl group departs from conjugation to some extent. The introduction of a voluminous substituent into position 2 should disturb this conjugation substantially and thereby give information on the fine structure of the molecule. In view of this, we have performed the synthesis of a number of sterically hindered 3-acylindoles.

3-Formyl-2-alkylindoles were obtained by the Vilsmeier formylation of 2-methyl- and 2-tert-butylindoles. In this process there is no possibility of the prolonged elimination of the dimethylamine formed, as described for indole itself; the reaction products crystallize very rapidly in a fairly pure state. The substituents in position 2 have a substantial influence on the yield of the reaction product. Thus, on passing from 2-methylindole to 2-tert-butylindole the yield falls by 15%. This influence is still more considerable on acetylation with dimethylacetamide where the steric requirements of the reagent are considerably greater. While 2-methylindole acetylates with a yield of 75%, the reaction with 2-tert-butylindole under the same conditions takes place to the extent of only 5%. An increase in the time of the reaction and a raising of its temperature did not lead to an improvement in the yield.

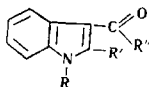


The introduction of a bromine atom into position 5 of the indole molecule obstructs acylation in position 3; the action of dimethylformamide and of phosphorous oxychloride on 5-bromo-2-methylindole leads to only 75% formylation, while for 2-methylindole the yield under the same conditions is 95%. There is practically no acetylation of 5-bromo-2-methylindole under the action of dimethylacetamide and phosphorous oxychloride, only traces of 3-acetyl-5-bromo-2-methylindole being formed. This is apparently a re-

\* For Communication XVII, see [2].

† Probationer from Sofia University, Bulgaria.

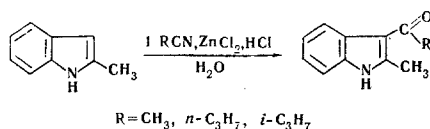
TABLE 1. Absorption Maxima in the IR Spectra of 3-Acylindoles (1700-1550  $\text{cm}^{-1}$  region, in paraffin oil)



R	R'	R''	$\nu_{\text{C=O}}$ , $\text{cm}^{-1}$
H	H	H	1638, 1618
CH <sub>3</sub>	H	H	1620, 1590
H	CH <sub>3</sub>	H	1620, 1590
CH <sub>3</sub>	CH <sub>3</sub>	H	1648
H	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	1625, 1590 (in CHCl <sub>3</sub> 1645)
H	H	CH <sub>3</sub>	1625, 1590
H	CH <sub>3</sub>	CH <sub>3</sub>	1620, 1590
H	CH <sub>3</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	1630, 1620 (in CHCl <sub>3</sub> 1655)
H	CH <sub>3</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	1617, 1590
H	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	CH <sub>3</sub>	1635

sult of the I effect of the halogen atom in position 5 of the benzene part of the molecule, from which the influence of substituents is transferred particularly strongly to the pyrrole part of the indole nucleus [1].

The Hoesch synthesis enabled an acetyl group to be introduced into position 3 of 2-methylindole, and under more severe conditions it was possible to acylate 2-methylindole with butyronitrile and isobutyronitrile, giving 3-butyryl and 3-isobutyryl-2-methylindoles. The use of the nitrile with the sterically more hindered nitrile group sharply lowers the yield of acyl derivative (from 78 to 25% under identical conditions).



When dry hydrogen chloride is passed through an ethereal solution of 2-*tert*-butylindole and acetonitrile (the usual conditions of the Hoesch reaction), a salt-like compound separates out which is converted quantitatively by the action of water or triethylamine into the initial 2-*tert*-butylindole. This salt-like compound is apparently the product of the protonation of 2-*tert*-butylindole, since its PMR spectrum (in CF<sub>3</sub>COOH) has the signal of an aliphatic methylene group (4.41 ppm) and the singlet signal of a *tert*-butyl group (1.50 ppm).

By the acylation of 2-methylindole with diketene, followed by hydrolysis, we obtained a good yield of 3-acetyl-2-methylindole, but it was impossible to acylate 2-*tert*-butylindole in position 3 by this method either, which confirms the considerable steric hindrance to electrophilic attack in this compound. Thus, both diketene and the imidic chloride (in the Hoesch synthesis) present high steric demands.

2-*tert*-Butylindole, position 3 of the indole nucleus of which cannot be attacked by these reagents for steric reasons, can be acylated only by means of the Vilsmeier reagents. It is possible that here, also, there is competition with protonation. A proton, the steric demands of which are minimal, attacks the indole nucleus primarily but, in the case of 2-*tert*-butylindole, this process takes place far more rapidly than the attack of the acylium cation or of analogous reagents, and the carbocation formed leaves the reaction sphere in the form of salt.

In a number of papers on the IR spectroscopy of 3-acylindoles, attempts have been made to assign the frequencies in the 1550-1680  $\text{cm}^{-1}$  region and to isolate the intrinsic frequencies of the vibrations of the carbonyl group [3, 4]. However, when a long chain of conjugation is present in this type of structure, which are vinyls of amides, it is extremely difficult to make this type of assignment (see, for example, [5]). The IR spectra of the 3-acylindoles that we obtained have doublets in the 1580-1640  $\text{cm}^{-1}$  region (in paraffin oil; see Table 1). This is in harmony with previous [3] information for 3-acylindoles. On passing from paraffin oil to chloroform or dioxane, the doublet nature of the absorption disappears. This doublet is apparently connected with the absorption of the carbonyl group and is determined by the crystal packing of the molecules in the solid state. In solution, the band is shifted by 30-40  $\text{cm}^{-1}$  in the high-frequency direction, which is due to the presence of intermolecular hydrogen bonds in the solid state. Even in solution,

this signal, which may be assigned to the carbonyl group, is not symmetrical, and on careful investigation a shoulder is found.

The introduction of a methyl group into position 1 can hardly affect the carbonyl position sterically, but it can change the degree of conjugation and exclude a hydrogen bond. In actual fact, on passing from 3-formyl-2-methylindole to 3-formyl-1,2-dimethylindole the region of the absorption of the carbonyl group shifts by  $30\text{ cm}^{-1}$  in the high-frequency direction and its doublet nature disappears.

The spectrum of 3-acetyl-2-*tert*-butylindole, which has only one band ( $1635\text{ cm}^{-1}$ ) even when the spectrum is recorded in paraffin oil, is somewhat anomalous.

In view of the possibility of serious errors in the assignment of the frequencies for this type of conjugated structures, we have been unable, on the basis of the results of IR spectroscopy, to give an evaluation of the steric arrangement of acyl groups in the 3-acylindoles. This question will be the subject of a special investigation.

## EXPERIMENTAL

In all cases, the purity of the substances was checked by thin-layer chromatography [alumina of activity grade II; benzene-ethanol (9:1) system].

**2-*t*-Butyl-3-formylindole.** 2.3 ml (0.03 mole) of freshly distilled dimethylformamide was cooled with a mixture of ice and salt for 30 min, and then, with stirring, 0.7 ml (0.008 mole) of freshly distilled phosphorous oxychloride was added dropwise over 30 min. The solution became yellow, and over an hour a solution of 1.2 g (0.007 mole) of 2-*t*-butylindole in 0.9 ml of dimethylformamide was added to it, the temperature being kept at 0 to  $5^{\circ}\text{C}$ . The well-stirred viscous reaction mixture was heated to  $35^{\circ}\text{C}$ , stirred for 1 h 30 min at this temperature, and treated with 4 g of crushed ice. Then it was poured into a 250-ml flask and 2 g of ice and, with vigorous stirring, 15 ml of 20% caustic soda solution were added. Stirring was continued for another 30 min, and the precipitate that had deposited was filtered off, carefully washed with water, and dried. Yield 1.1 g (80%), mp  $224^{\circ}\text{C}$ . After recrystallization from ethanol, the melting point did not change. Found %: C 77.72; H 7.46.  $\text{C}_{13}\text{H}_{15}\text{NO}$ . Calculated %: C 77.61; H 7.46. Colorless crystals readily soluble in pyridine, dioxane, and dimethyl sulfoxide, less readily in ethanol and acetone.

**3-Formyl-2-methylindole** was obtained similarly from 2 g (0.015 mole) of 2-methylindole, 7.2 ml (0.093 mole) of dimethylformamide, and 1.53 ml (0.0167 mole) of phosphorus oxychloride. Yield 2.2 g (95%), mp  $204^{\circ}\text{C}$  (from ethanol). Literature data [6]: mp  $200^{\circ}\text{C}$ .

**5-Bromo-3-formyl-2-methylindole** was synthesized in the same way, but the addition of the solution of 5-bromo-2-methylindole was carried out at  $6-7^{\circ}\text{C}$ . The yield of substance from 1 g (0.005 mole) of 5-bromo-2-methylindole, 2.3 ml (0.03 mole) of dimethylformamide, and 0.5 ml (0.005 mole) of phosphorus oxychloride was 1.1 g (75%), mp  $263^{\circ}\text{C}$  (from ethanol). Found %: C 50.11; H 3.35.  $\text{C}_{10}\text{H}_8\text{BrNO}$ . Calculated %: C 50.42; H 3.36.

**3-Butyryl-2-methylindole.** A solution of 4 g (0.03 mole) of 2-methylindole in 6 ml of absolute ether was treated with 4.1 g (0.06 mole) of butyronitrile and catalytic amounts of anhydrous zinc chloride, after which dry hydrogen chloride was passed through the mixture for 14 h. The solution gradually became viscous and acquired a dark red color. It was left overnight, and the crystalline substance that had deposited was filtered off, washed with ether, and dissolved in water, and the solution was brought to the boil and treated with a few drops of aqueous ammonia solution. An oil separated out which, on further boiling, solidified. After crystallization from ethanol, 3.5 g (78%) of 3-butyryl-2-methylindole with mp  $150-154^{\circ}\text{C}$  was obtained. Found %: C 77.51; H 7.46.  $\text{C}_{13}\text{H}_{15}\text{NO}$ . Calculated %: C 77.61; H 7.46.

**3-Isobutyryl-2-methylindole.** A solution of 4 g (0.03 mole) of 2-methylindole in 14 ml of absolute ether was treated with 4.6 g (0.065 mole) of isobutyronitrile and a catalytic amount of dry zinc chloride, and a current of dry hydrogen chloride was passed through the mixture for 12 h. The solution first became turbid and then a dark red oil separated out which went into solution again with the further passage of hydrogen chloride. After the end of the passage of HCl, a small amount of a crystalline substance deposited from the solution; this was filtered off and, after hydrolysis in the presence of 25% ammonia solution, 150 mg of 3-isobutyryl-2-methylindole was obtained. The ethereal filtrate was extracted twice with water, and the aqueous extract was filtered and, after the addition of ammonia, heated to the boil. This gave an additional 1.3 g

of 3-isobutyryl-2-methylindole. The total yield was 25%, mp 186°C, pale yellow crystals, readily soluble in pyridine and dioxane, less readily in chloroform, acetone, and ethanol. Found %: C 77.22; H 7.51. C<sub>13</sub>H<sub>15</sub>NO. Calculated %: C 77.61; H 7.46.

The other 3-acylindoles were synthesized by known methods.

#### LITERATURE CITED

1. A. N. Kost, V. I. Minkin, R. S. Sagitullin, V. I. Gorbunov, and I. D. Sadekov, ZhOKh (in press).
2. A. N. Kost, V. V. Eraksina, E. V. Vinogradova, and T. S. Khazanova, KhGS [Chemistry of Heterocyclic Compounds], 2, 226 (1966).
3. W. Anthony, J. Org. Chem., 25, 2049 (1960).
4. F. Millich and G. Becker, J. Org. Chem., 23, 1096 (1958).
5. A. Ya. Strakov, M. T. Strautzele, I. A. Strakova, and E. Yu. Gudrinietse, Izv. AN Latv.SSR, Ser. Khim., 563 (1967).
6. R. Seka, Ber., 56, 2060 (1923).