INDOLE DERIVATIVES. LIV†. SYNTHESIS OF 3, 5-DIACETYLINDOLE

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3, 5-Diacetylinodole has been synthesized by three routes: acetylation of 5-acetylindole with acetic anhydride; reaction of 5-acetylindole with dimethylacetamide in the presence of phosphoryl chloride; and cyclization of biacetyl p-acetylphenylhydrazone with polyphosphoric acid. 5-Acetylindole was obtained by cyclizing ethyl pyruvate p-acetylphenylhydrazone.

Ketones of the indole series are fairly well known, but it would be interesting to obtain diacylindoles, with an acyl group in each of the benzene and pyrrole rings. Such ketones would offer further possibilities in the search for new biologically active compounds. They could, in addition, be used for the synthesis of monomers containing indole nuclei. For these reasons, we have synthesized 3, 5-diacetylindole.

Attempts were first made to obtain the desired ketone from 1, 3-diacetylindole by the Friedel-Crafts reaction, but these attempts were unsuccessful. Treatment of 1, 3-diacetylindole with acetic anhydride of acetyl chloride in presence of aluminum chloride, zinc chloride, or boron trifluoride etherate led either to recovery of starting material or, under more severe conditions, to the formation of resins from which no pure compound could be isolated.

In subsequent experiments, we used 5-acetylindole (IX) as starting material. The preparation of this by the indoline-indole method has been described [1]. We synthesized 5-acetylindole in about the same yield by another method, utilizing the Japp-Klingemann reaction.

p-Nitroacetophenone (I) was reduced in the usual way, and the diazonium salt (III) obtained from p-aminoacetophenone (II) was coupled with ethyl methylacetoacetate. The Japp-Klingemann reaction with p-acetylphenyldiazonium chloride did not proceed cleanly. The main reaction product was ethyl pyruvate p-acetylphenylhydrazone (IV), mp 154-155°, the structure of which is considered below. Biacetyl p-acetylphenylhydrazone (V) was formed in small amount. If the ethyl methylacetoacetate was first hydrolyzed, as in the preparation of biacetyl phenylhydrazone [2], then V was the sole reaction product. A third reaction product was identical with 3-ethoxycarbonyl-1, 5-bis-(p-acetylphenyl)formazan (VI), which was obtained by an independent synthesis from acetoacetic ester and p-acetylphenyldiazonium chloride. The formation of VI may be explained by the presence of a small amount of ethyl acetoacetate in the ethyl methvlacetoacetate (which was obtained from dimethylaminocrotonic ester [3]).

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† For Part LIII, see [10].

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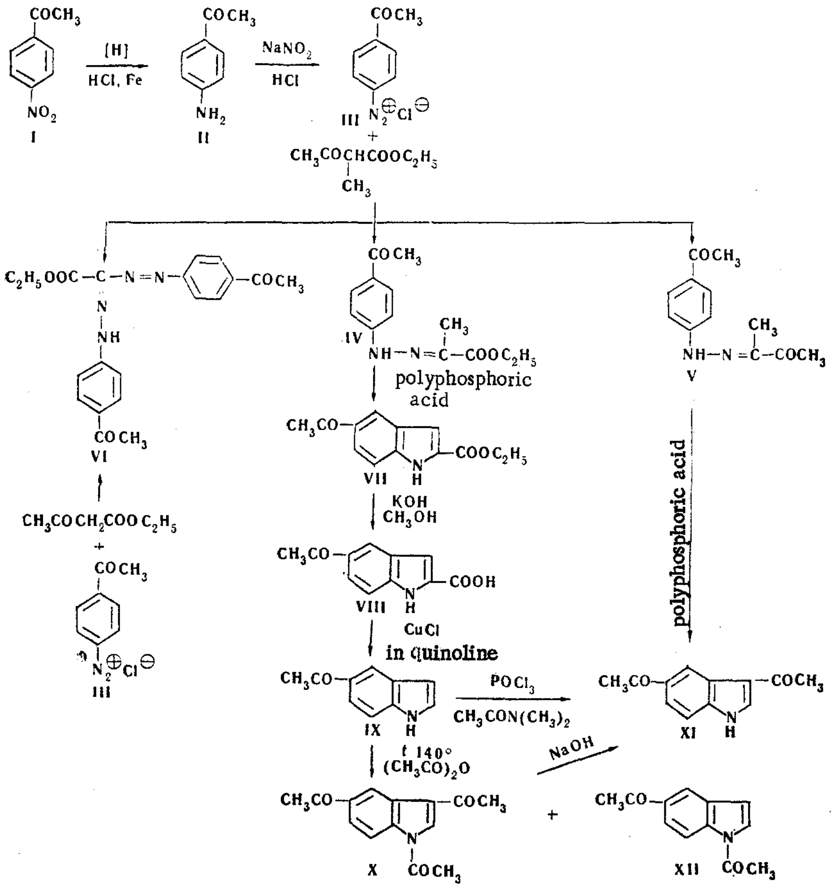
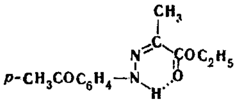
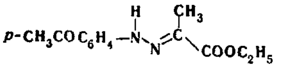


On heating IV in isopropanol in the presence of sulfosalicylic acid, or in glacial acetic acid saturated with dry hydrogen chloride, and also by heating with a fivefold excess of zinc chloride, the hydrazone isomerises to give in every case both the starting material, and its stereoisomer, mp 119-120°, in approximately equal amounts. Ethyl pyruvate phenylhydrazone is known to exist as the syn- and anti-isomers [4]. The syn- or anti-structure may be assigned to each isomer by IR spectroscopy [5]. We assign the syn-configuration IVa to the lower-melting isomer, mp 119-120°, which is readily soluble in organic solvents, and the anti-configuration IVb to the Japp-Klingemann reaction product, mp 154-155°. These assignments were confirmed by the IR spectra. The anti-isomer, IVb showed two bands due to N−H stretching, one at 3290 cm^{-1}, and the other, less intense, at 3190 cm^{-1}. The syn-isomer exhibited only one band, at 3250 cm^{-1}. Two bands (1700 and 1660 cm^{-1}) were observed for the C=O stretching in the case of the anti-isomer, but only one (1680 cm^{-1}) in the case of the syn-isomer.

Only in the presence of polyphosphoric acid were we able to cyclize the hydrazone IV to ethyl 5-acetylindole-2-carboxylate (VII). This was hydrolyzed with alcoholic alkali, and decarboxylated by heating with cuprous chloride in quinoline to give 5-acetylindole (IX), which was identical with a sample obtained by the literature method [1].



IVa



IVb

The acetyl group was introduced into the pyrrole ring by two methods: acetylation of 5-acetylindole with acetic anhydride, followed by hydrolysis of the resulting 1, 3, 5-triacetylindole (X), and by the Vilsmier reaction. In the first case, in addition to X, 1, 5-diacetylindole (XII) was formed in small amounts. Mild alkaline hydrolysis converted this into 5-acetylindole.

Thus, the presence of an acetyl group in the 5-position of the benzene ring does not hinder acetylation of the pyrrole ring. This occurs in the 3-position, as shown by the PMR spectrum. In the spectrum of 3,5-diacetylindole (XI) in trifluoroacetic acid, signals due to the protons of the acetyl groups are observed at δ 2.92 and 3.02 ppm; to the protons of the benzene ring at δ_4 9.04, δ_6 8.22; and δ_7 7.77 ppm; and to the two protons of the pyrrole ring, at δ_1 11.19 and δ_2 8.76 ppm, the latter having a coupling constant of $J_{H_1H_2}$ = 4.5 Hz.

An attempt was made to obtain 2, 5-diacetylindole by cyclizing biacetyl p-acetylphenylhydrazone (V) in polyphosphoric acid. However, the product of the reaction was 3, 5-diacetylindole. A similar result has been observed in the cyclization of biacetyl monophenylhydrazone in polyphosphoric acid [6].

Reaction of the diketone XI with hydroxylamine gives the dioxime, whereas thiosemicarbazide furnished only the mono derivative. This was shown to be the 5-thiosemicarbazone, by its IR spectrum, which showed a band due to the 3-carbonyl group. The reactivity of the latter is probably reduced by virtue of its vinylogous amide character.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument, as suspensions in Vaseline oil (unless a solvent is mentioned specifically). The UV spectra were taken with an SF-4A instrument, in alcoholic solution. The PMR spectra were taken on a JNM-4H-100 instrument, using trifluoroacetic acid as solvent and tetramethylsilane as internal standard.

The compounds prepared were identified by thin layer chromatography on grade II alumina.

Reaction of p-Acetylphenyldiazonium Chloride with Ethyl Methylacetoacetate. 15 g (0.11 mole) of p-aminoacetophenone [7] (II) in 54 ml of water and 10.8 ml of concentrated hydrochloric acid was heated until solution occurred. Then the solution was poured into 34.2 ml of cold, concentrated hydrochloric acid, with stirring. Sodium nitrite (8.5 g, 0.12 mole) in 18 ml of water was then added during 20 min at 0 to -3°.

A 50% solution of potassium hydroxide (38.4 ml) was added with stirring to 15.75 g (0.11 mole) of ethyl methylacetoacetate [3] in 115 ml of ethanol. The mixture was diluted with 230 ml of ice water, and the cold (-3°) solution of the diazonium salt was added quickly with stirring. Stirring was continued for a further 15 min, the bulk of the reaction product separating as heavy, dark-colored lumps. A small amount of colorless crystals suspended in water was filtered off to give 0.7 g of biacetyl mono-p-acetylphenylhydrazone (V), mp 196-197° (from ethanol). R_f 0.62 (benzene:acetone, 7:3). Found: C 66.30; 66.49; H 6.52; 6.59; N 12.82; 12.78%. $C_{12}H_{14}N_2O_2$. Calculated: 66.05; H 6.42; N 12.82%.

The dark-colored crystals were then filtered off and recrystallized from benzene to give 16 g (58%) of ethyl pyruvate p-acetylphenylhydrazone (IV), mp 154-155°, R_f 0.62 (benzene:acetone, 7:3). Found: C 63.05; 63.04; H 6.62, 6.51; N 11.57, 11.39%. $C_{13}H_{16}N_2O_3$. Calculated: C 62.90; H 6.46; N 11.30%.

From the benzene mother liquors was isolated 0.8 g of the cherry-red 3-ethoxycarbonyl-1, 5-bis-(p-acetylphenyl)formazan (VI), mp 195-197° (from alcohol), R_f 0.76 (benzene:acetone, 7:3). This was identical with an authentic specimen, obtained as described below.

3-Ethoxycarbonyl-1, 5-bis-(p-acetylphenyl)formazan (VI). This compound was obtained in a similar way to 3-ethoxycarbonyl-1, 5-diphenyl-formazan [8]. 2.59 g (0.019 mole) of II was dissolved with heating in 18 ml of water and 3.81 ml of concentrated hydrochloric acid, then cooled to 0° with stirring. To the resulting suspension was added at 0° 1.32 g of sodium nitrite (0.019 mole) in 2.5 ml of water, followed by a solution of 7.5 g of potassium acetate in 75 ml of water. To the resulting solution was added dropwise at 0° to –3° with vigorous stirring a freshly prepared solution of 1.25 g (0.096 mole) of ethyl acetoacetate in 25 ml of cold 10% potassium hydroxide. The mixture was stirred for 3 h at 0-3°, then the precipitate was filtered off, washed well with water, and dried on a porous plate to give 2.7 g (40%) of a dark-colored material, mp 189-192° (from alcohol). IR spectrum: 1520, 1600, 1680, and 1720 cm^{-1}. Found: C 63.18; 62.99; H 5.29; 5.10; N 14.91; 15.08%. $C_{20}H_{20}N_4O_4$. Calculated: C 63.15; H 5.26; N 14.73%.

Isomerization of Ethyl Pyruvate p-Acetylphenylhydrazone (IVb). To 1 g (0.004 mole) of the hydrazone IVb was added a solution of 1.5 g of sulfosalicylic acid in 13.5 ml of isopropanol and 1.35 ml of water. The mixture was boiled for 1 h 30 min, cooled, and poured into 50 ml of water. The resulting yellow precipitate was filtered off to give 0.8 g of material. Thin layer chromatography in benzene-acetone (4:1) gave a spot at R_f 0.40 (starting material), and one at R_f 0.89. Crystallization from alcohol gave 0.3 g of the stereoisomer IVa with R_f 0.89, mp 119-120°. Found: C 62.76; 62.76; H 6.57; 6.58; N 11.45; 11.57%. $C_{13}H_{16}N_2O_3$. Calculated C 62.90; H 6.46; N 11.30%. From the alcoholic mother liquors there was isolated 0.28 g of IVb.

Ethyl 5-acetylindole-2-carboxylate (VII). To polyphosphoric acid, obtained from 16.5 ml of orthophosphoric acid (d^{18} 1.725) and 25.15 g of phosphoric anhydride [9], was added 6 g (0.024 mole) of IV. The mixture was gradually heated to 95° (in a bath), whereupon the temperature rose rapidly to 115-120°. After 5 min, the mixture was cooled to 5°, the oil was triturated with ice (400 g), and the greenish crystalline product was filtered off to give 4.6 g (83%), mp 138-139° (from heptane). IR spectrum: 1620 and 1670 cm^{-1} (C=O), 3330 cm^{-1} (N–H). Found: C 67.28; 66.93; H 5.73; 5.87; N 6.14; 6.33%. $C_{13}H_{13}NO_3$. Calculated: C 67.53; H 5.63; N 6.07%.

5-Acetylindone-2-carboxylic Acid (VIII). A mixture of 2 g (8.7 mmole) of the ester VII and 5 g of potassium hydroxide in 25 ml of methanol was boiled for 3 h. Most of the methanol was distilled off, and the residue was acidified with dilute hydrochloric acid (1:1). The colorless precipitate which separated was filtered off to give 1.78 g (quantitative yield), mp 270° (from acetone-heptane). Found: C 65.15; 64.96; H 4.22; 4.29; N 7.07; 7.06%. $C_{11}H_9NO_3$. Calculated: C 65.00; H 4.44; N 6.90%.

5-Acetylindole (IX). 1.5 g (7.4 mmole) of the acid VIII was triturated with 1 g of cuprous chloride, and 30 ml of quinoline which had been redistilled over barium oxide was added. The mixture was heated with stirring at 185-190° for 1 h, then it was boiled for 30 min. After cooling, the mixture was poured into 100 ml of cold 10% hydrochloric acid, and extracted repeatedly with ether (500 ml in all). The ether extracts were washed with water, sodium bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. The oily material which remained after removal of the ether was crystallized from heptane to give 0.5 g (44%) of 5-acetylindole (IX), mp 97.5-99° (lit. [1], mp 94-95°). IR spectrum: 1660 cm^{-1} (C=O) and 3300 cm^{-1} (N–H).

3, 5-Diacetylindole (XI). a) A mixture of 1.35 g (8.5 mmole) of IX and 15 ml of freshly distilled acetic anhydride was boiled for 30 h. On cooling, 1.55 g (75%) of crystals of 1, 3, 5-triacetylindole (X) separated, mp 218° (from heptane), R_f 0.57 (benzene–acetone, 8:2). The IR spectral band at 1720 cm^{-1} may be due to the stretching of the carbonyl group on nitrogen, and that at 1670 cm^{-1} to the C=O groups in the 3- and 5-positions. UV spectrum: λ_{max} 243 nm (log ε 4.43), and 296 nm (log ε 3.73). Found: C 68.83; 68.82; H 5.62, 5.67; N 5.78, 5.63%. $C_{14}H_{13}NO_3$. Calculated %: C 69.10; H 5.35; N 5.76%.

Evaporation of the mother liquors gave 0.15 g of colorless crystals of 1, 5-diacetylindole (XII), mp 147-148° (from heptane, then alcohol). R_f 0.78 (benzene-methanol, 9:1). In the IR spectrum, stretching of the 1–C=O was observed at 1705 cm^{-1}, and of the 5–C=O at 1668 cm^{-1}; the N–H stretching frequency occurred at 3110-3175 cm^{-1} as a broad band with three maxima. λ_{max} 250 nm (log ε 4.56). Found: C 71.85; 72.05; H 5.72; 5.78; N 6.83; 6.70%. $C_{12}H_{11}NO_2$. Calculated: C 71.58; H 5.47; N 6.97%.

0.5 g (2.6 mmole) of X was dissolved in 5 ml of ethanol and 2.5 ml of 2N NaOH with heating, and the mixture was boiled for 2 min. Water was added to the cooled mixture to precipitate 3, 5-diacetylindole (XI). The yield was quantitative, recrystallized from isopropanol. It was further purified by sublimation, mp 256-257°, R_f 0.22 (benzene-acetone, 8:2). UV spectrum: λ_{max} 244 nm (log ε 4.66) and 296 nm (log ε 4.11). Found: C 71.34; 71.34; H 5.52; 5.70; N 7.22; 7.24%. $C_{12}H_{11}NO_2$. Calculated: C 71.58; H 5.47; N 6.97%.

b) To a mixture of 1.6 g (0.01 mole) of IX and 2.6 g of dimethylacetamide was added dropwise with vigorous stirring and ice-cooling 2.3 g of phosphoryl chloride at such a rate that the temperature did not exceed 20°. The mixture was stirred for 1 h at this temperature, then for a further h at 50-55°. After cooling, the reaction mixture was treated with 20 ml of ice-water, with stirring. The precipitate was isolated, and the filtrate was treated with 0.5 N NaOH to pH 6. The crystals which separated were filtered off and sublimed to give 0.2 g (10%) of XI, mp 254-256°.

c) To 16.5 ml of polyphosphoric acid was added 2 g (9.2 mmole) of the hydrazone V. The mixture was heated gradually to 120-130°, and kept at this temperature for 1 h 30 min. After cooling to 3°, the mixture was poured onto ice (400 g). The dark brown precipitate was dried, extracted with 200 ml of hot benzene, nearly all the benzene distilled off, and the residue treated with light petroleum to precipitate yellow crystals which were dried and sublimed to give 0.2 g (11%) of XI, mp 250-252°.

The mp's of mixtures of the materials obtained by methods b) and c) with that obtained by method a) were underpressed. The R_f values of the three materials were identical, as were their IR spectra.

3, 5-Diacetylindole Dioxime. A mixture of 0.2 g (1 mmole) of XI, 0.32 g (4.6 mmole) of hydroxylamine hydrochloride, and 0.96 g (12 mmole) of sodium acetate in 25 ml of ethanol and 10 ml of water was boiled for 7 h. The alcohol was distilled off, and the crystals which separated were filtered off to give 0.2 g (87%), mp 212° (decomp., from aqueous alcohol). Found: N 17.85; 17.73%. $C_{12}H_{13}N_3O_2$. Calculated: N 18.18%.

3, 5-Diacetylindole 5-Monothiosemicarbazone. A mixture of 0.2 g (1 mmole) of XI and 0.2 g (2.2 mmole) of thiosemicarbazide in 28 ml of ethanol was boiled for 9 h. Half the alcohol was distilled off, and the crystals which separated were filtered off to give 0.27 g (99%), mp 190° (decomp., from alcohol). Found: N 20.67; 20.83; S 11.92; 11.99%. $C_{13}H_{14}N_4OS$. Calculated: N 20.42; S 11.70%.

LITERATURE CITED

1. A. P. Terent'ev, M. N. Preobrazhenskaya, and G. M. Sorokina, ZhOKh, 29, 2875 (1959).
2. F. Japp and F. Klingemann, J. Chem. Soc., 519 (1888).
3. E. A. Mistryukov, Izv. AN SSSR, OKhN, 1512 (1961).
4. V. Klein and P. de la Mare (eds.) Progress in Stereochemistry [Russian translation], IL, Moscow. 231 (1961).
5. M. N. Preobrazhenskaya, N. V. Uvarova, Yu. N. Sheinker, and N. N. Suvorov, DAN, 148, 1088 (1963).
6. Chang Ming-che, and He Tsung-yim, Acta Chim. Sinica, 32, 64 (1966); RZhKh, 1Zh289 (1967).
7. V. B. Drewsen, Ann., 212, 162 (1882).
8. E. Bamberger and E. W. Wheelwright, J. Pract. Chem., 65, 125 (1902).
9. D. Fritzuhlig, Angew. Chem. 66, 435 (1954).
10. Yu. I. Sushkevich, V. E. Zhigachev, A. V. Sulima, and N. N. Suvorov, KhGS, 1076 (1970).