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SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF 2-(4-AMINO-2-METHYL-1H-INDOL-3-YL)- AND 2-(6-AMINO-2-METHYL-1H-INDOL-3-YL)ACETIC ACIDS

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A method was developed for the production of indole compounds containing an amino group at positions 4 and 6 of the benzene ring on the basis of the indolization of the 3-acetylaminophenylhydrazone of ethyl levulinate. A series of derivatives of 2-(4-amino-2-methyl-1H-indol-3-yl)- and 2-(6-amino-2-methyl-1H-indol-3-yl)acetic acids at the 4- and 6-amino group were synthesized.

Keywords: N-(3-hydrazinophenyl)acetamide, indole, indomethacin, Fischer reaction.

Earlier [1] we described the synthesis of derivatives of 2-(5-amino-2-methyl-1H-indol-3-yl)acetic acid. The present work was devoted to the synthesis of derivatives of 2-(2-methyl-1H-indol-3-yl)acetic acid containing an amino group at positions 4 and 6 of the benzene ring. It continues the research into the production of analogs of the well-known antiinflammatory drug indomethacin (2-[2-methyl-5-methoxy-1-(4-chlorobenzoyl)-1H-indol-3-yl]acetic acid) containing substituted amino groups instead of the methoxy group in the benzene ring with position 1 free.

The familiar method of introducing an amino group into the benzene ring of indole compounds by the cyclization of nitrophenylhydrazones followed by reduction of the nitro group cannot be used to obtain compounds with the amino group at positions 4 and 6. Nitration of 2-substituted indoles leads to the 5-nitro derivatives [4] and also cannot be used to introduce the amino group at positions 4 and 6.

The method that we are proposing makes it possible to produce 4- and 6-substituted derivatives of indole on the basis of the readily available 3-acetylaminophenylhydrazine. This amine was converted in two stages into the tin salt of N-(3-hydrazinophenyl)acetamide **2**. The isolation of free hydrazine from this salt is accompanied by resin formation, and its hydrazones are also unstable. We therefore brought the salt **2** directly into the Fischer reaction and obtained a mixture of the 4- and 6-acetylamino derivatives **3a**,**b** without isolating the intermediately formed hydrazone.

The isomer **3b** predominates in this mixture. This agrees with the report in [5] about the predominance of the 6-substituted indoles during the Fischer cyclization of phenylhydrazones containing electron-donating substituents at the *meta* position to the hydrazo group.

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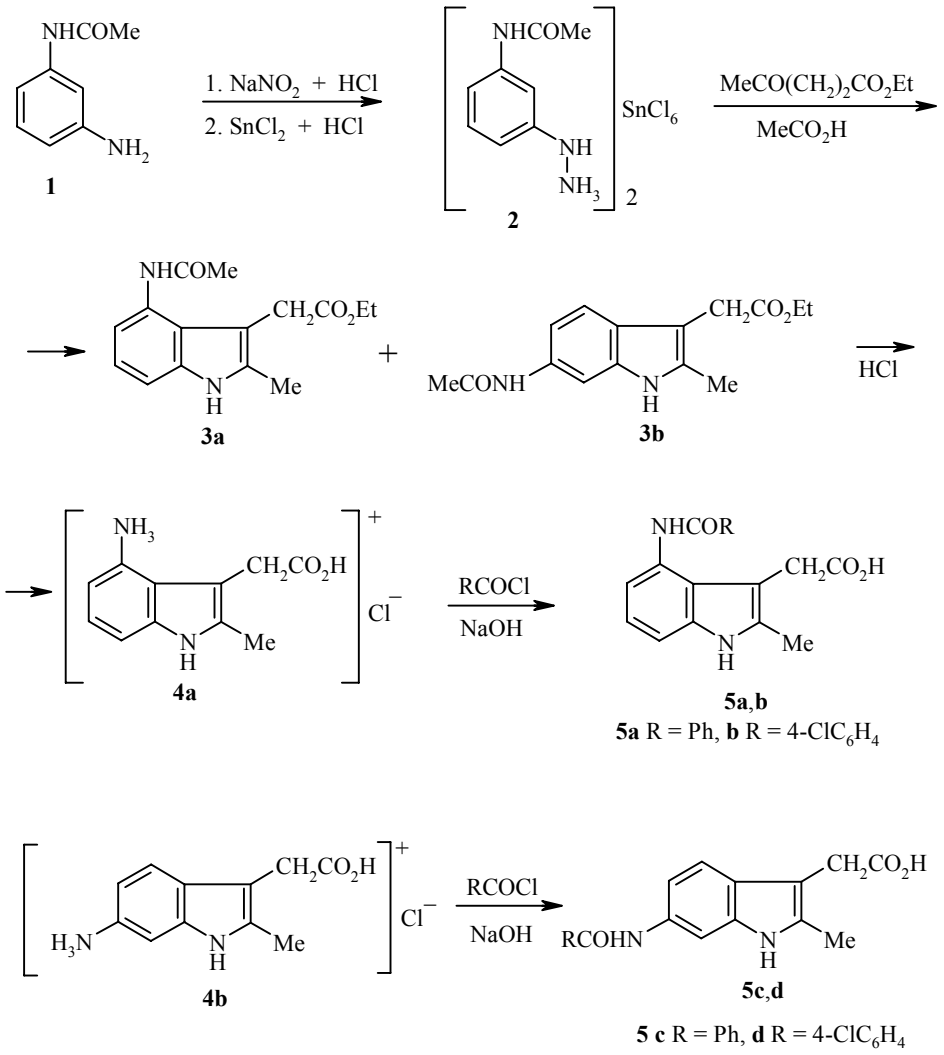

We were able to separate the mixture of these isomers – ethyl 2-[6-(acetylamino)-2-methyl-1H-indol-3-yl]acetate (**3b**) and ethyl 2-[4-(acetylamino)-2-methyl-1H-indol-3-yl]acetate (**3a**) – effectively. It was found that if the reaction mass after cyclization was treated with water most of the 6-isomer was precipitated while the 4-isomer could be extracted from the filtrate.

Removal of the N-acetyl protection with dilute hydrochloric acid led to 3-(carboxymethyl)-2-methyl-1H-indole-4(6)-ammonium chlorides (**4a**,**b**). The reaction here is not accompanied by resin formation. This makes it possible to synthesize various derivatives with respect to the amino group on the basis of the obtained compound.

Thus, it is possible by our proposed method to obtain indole compounds with the amino group at positions 4 and 6 of the benzene ring.

In order to carry out biological trials on the basis of compounds **4a**,**b** we synthesized 2-[4-(benzoylamino)-2-methyl-1H-indol-3-yl]- (**5a**), 2-[6-(benzoylamino)-2-methyl-1H-indol-3-yl]- (**5c**), 2-{4-[(4-chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}- (**5b**), and 2-{6-[(4-chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}acetic acid (**5d**).

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker WP-200 instrument (200 MHz) in acetone-d_6 for **3a**,**b** and DMS0-d_6 for **4a**,**b**, **5a-d** with TMS as internal standard. Analysis by TLC was conducted on Silufol UV-254 plates.

2-[3-(Acetylamino)phenyl]hydrazinium Tin Salt (2). A 20-g sample (0.13 mol) of N-(3-aminophenyl)acetamide (**1**) was diazotized by the method described in [6]. The obtained solution of the diazonium salt was added dropwise to a solution of $SnCl_2$ (54.4 g, 0.46 mol) in concentrated hydrochloric acid (50 ml), cooled to -12°C, so that the temperature did not rise above -10°C. The mixture was stirred for 30 min and left overnight in the refrigerator to complete the reaction. The precipitate was filtered off and dried over phosphorus pentoxide in a vacuum desiccator. Yield 25 g (28%). The compound was used without further purification.

Ethyl 2-[6-(Acetylamino)-2-methyl-1H-indol-3-yl]acetate (3b). A mixture of glacial acetic acid (100 ml), compound **2** (10 g, 0.015 mol), and ethyl levulinate (2.16 g, 0.015 mol) was boiled in a stream of argon for 1.5 h. The reaction mixture was cooled and filtered. Most of the acetic acid was removed on a rotary evaporator, and the residue was poured into water. The precipitate was filtered off, and 2.14 g (52%) of compound **3b** was obtained; mp 210-212°C (2-propanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.18 (3H, t, $J_{CH_3–CH_2}$ = 7.4, $CH_2–C\underline{H}_3$); 2.05 (3H, s, $CO–CH_3$); 2.38 (3H, s, CH_3); 3.62 (2H, s, CH_2); 4.06 (2H, m, $C\underline{H}_2–CH_3$); 6.97 (1H, d, J_{54} = 8.5, 5-H); 7.34 (1H, d, J_{45} = 8.5, 4-H); 7.99 (1H, s, 7-H); 9.01 (1H, s, NH_{amide}); 9.89 (1H, s, NH_{indole}). Found %: C 65.74; H 6.65; N 10.16. $C_{15}H_{18}N_2O_3$. Calculated %: C 65.68; H 6.61; N 10.21.

Ethyl 2-[4-(Acetylamino)-2-methyl-1H-indol-3-yl]acetate (3a). The filtrate from the synthesis of compound **3b** was extracted with propyl acetate (3 × 50 ml), washed with sodium bicarbonate solution and with water, and dried with sodium sulfate. The solvent was distilled under vacuum. We obtained 0.49 g (12%) of compound **3a**; mp 155-158°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.24 (3H, t, $J_{CH_3–CH_2}$ = 7.3, $CH_2–C\underline{H}_3$); 2.14 (3H, s, $CO–CH_3$); 2.41 (3H, s, CH_3); 3.81 (2H, s, CH_2); 4.16 (2H, m, $C\underline{H}_2–CH_3$); 6.96 (1H, dd, J_{67} = 7.3, J_{65} = 7.7, 6-H); 7.07 (1H, d, J_{56} = 7.7, 5-H); 7.45 (1H, d, J_{76} = 7.3, 7-H); 9.49 (1H, s, NH_{amide}); 10.15 (1H, s, NH_{indole}). Found %: C 65.72; H 6.68; N 10.18. $C_{15}H_{18}N_2O_3$. Calculated %: C 65.68; H 6.61; N 10.21.

3-(Carboxymethyl)-2-methyl-1H-indole-4-ammonium Chloride (4a). A mixture of compound **3a** (4.0 g, 0.0146 mol) and 18% hydrochloric acid (16 ml) was boiled for 45 min. The reaction mass was cooled, and the crystals were separated, washed with ether, and dried over phosphorus pentoxide in a vacuum desiccator. Yield 2.86 g (81%); mp 209°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.36 (3H, s, CH_3); 3.83 (2H, s, CH_2); 7.05 (2H, s, 5-, 6-H); 7.29 (1H, s, 7-H); 11.29 (1H, s, NH). Found %: C 54.92; H 5.48; Cl 14.67; N 11.58. $C_{11}H_{13}ClN_2O_2$. Calculated %: C 54.89; H 5.44; Cl 14.73; N 11.64.

3-(Carboxymethyl)-2-methyl-1H-indole-6-ammonium Chloride (4b). A mixture of compound **3b** (4.0 g, 0.0146 mol) and 18% hydrochloric acid (40 ml) was boiled for 45 min. The reaction mass was cooled, and the crystals were separated, washed with ether, and dried over phosphorus pentoxide in a vacuum desiccator. Yield 2.96 g (84%); decomp. 220°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.33 (3H, s, CH_3); 3.57 (2H, s, CH_2); 6.95 (1H, d, J_{54} = 8.1, 5-H); 7.36 (1H, s, 7-H); 7.45 (1H, d, J_{45} = 8.1, 4-H); 11.16 (1H, s, NH). Found %: C 54.93; H 5.49; Cl 14.65; N 11.57. $C_{11}H_{13}ClN_2O_2$. Calculated %: C 54.89; H 5.44; Cl 14.73; N 11.64.

2-[4-(Benzoylamino)-2-methyl-1H-indol-3-yl]acetic Acid (5a). To a solution of sodium hydroxide (0.52 g, 0.013 mol) and compound **4a** (1 g, 0.004 mol) in water (15 ml) while stirring and cooling on a water bath we added dropwise benzoyl chloride (0.7 g, 0.005 mol). The reaction mass was stirred for 1 h and acidified with hydrochloric acid, and the precipitate was filtered off. Yield 1.26 g (98%); mp 210-212°C (decomp., from methanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.32 (3H, s, CH_3); 3.62 (1H, s, CH_2); 6.98 (1H, t, J_{65} = J_{67} = 7.7, 6-H); 7.14-7.16 (2H, t, J_{56} = J_{76} = 7.7, 5-, 7-H); 7.50-7.54 (3H, m, 3-, 4-, 5-H, PhCO); 7.99 (2H, d, J_{23} = 7.3, 2-, 6-H, PhCO); 10.20 (1H, s, NH_{indole}); 10.90 (1H, s, NH_{amide}). Found %: C 70.19; H 5.27; N 9.12. $C_{18}H_{16}N_2O_3$. Calculated %: C 70.12; H 5.23; N 9.09.

2-{4-[(4-Chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}acetic Acid (5b). To a solution of sodium hydroxide (0.52 g, 0.013 mol) and compound **4a** (1 g, 0.004 mol) in water (15 ml) while stirring and cooling on a water bath we added dropwise 4-chlorobenzoyl chloride (0.82 g, 0.005 mol). The reaction mass was stirred for 1 h and acidified with hydrochloric acid. The precipitate was filtered off. Yield 1.3 g (94%); decomp. 205°C (methanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.32 (3H, s, CH_3); 3.60 (2H, s, CH_2); 6.98 (1H, t, $J_{65} = J_{67} = 7.7$, C(6)H); 7.12-7.15 (2H, t, $J_{56} = J_{76} = 7.7$, 5-, 7-H); 7.55 (2H, d, $J_{32} = 8.5$, 3-, 5-H, ClC_6H_4CO); 8.01 (2H, d, $J_{23} = 8.5$, 2-, 6-H, ClC_6H_4CO); 10.31 (1H, s, NH_{amide}); 10.91 (1H, s, NH_{indole}). Found %: C 63.15; H 4.52; Cl 10.28; N 8.23. $C_{18}H_{15}ClN_2O_3$. Calculated %: C 63.07; H 4.41; Cl 10.34; N 8.17.

2-[6-(Benzoylamino)-2-methyl-1H-indol-3-yl]acetic Acid (5c). To a solution of sodium hydroxide (0.75 g, 0.019 mol) and compound **4b** (1.4 g, 0.0058 mol) in water (20 ml) while stirring and cooling on a water bath we added dropwise benzoyl chloride (0.98 g, 0.007 mol). The reaction mass was stirred for 1 h and acidified with hydrochloric acid, and the precipitate was filtered off. Yield 1.6 g (62%); mp 220-222°C (decomp., from methanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.32 (3H, s, CH_3); 3.53 (2H, s, CH_2); 7.23 (1H, d, $J_{54} = 8.8$, 5-H); 7.32 (1H, d, $J_{45} = 8.8$, 4-H); 7.5 (3H, m, 3-, 4-, 5-H, PhCO); 7.87 (1H, s, 7-H); 7.97 (2H, d, $J_{23} = 8.8$, 2-, 6-H, PhCO); 9.95 (1H, s, NH_{amide}); 10.65 (1H, s, NH_{indole}). Found %: C 70.23; H 5.27; N 9.14. $C_{18}H_{16}N_2O_3$. Calculated %: C 70.12; H 5.23; N 9.09.

2-{6-[(4-Chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}acetic Acid (5d). To a solution of sodium hydroxide (0.52 g, 0.013 mol) and compound **3b** (1 g, 0.004 mol) in water (15 ml) while stirring and cooling on a water bath we added dropwise 4-chlorobenzoyl chloride (0.82 g, 0.005 mol). The reaction mass was stirred for 1 h and acidified with hydrochloric acid, and the precipitate was filtered off. Yield 1.15 g (90%); mp 226°C (decomp., from methanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.31 (3H, s, CH_3); 3.53 (2H, s, CH_2); 7.22 (1H, d, $J_{54} = 8.5$, 5-H); 7.32 (1H, d, $J_{45} = 8.5$, 4-H); 7.59 (2H, d, $J_{32} = 8.6$, 3-, 5-H, 4-ClC_6H_4CO); 7.89 (1H, s, 7-H); 8.00 (2H, d, $J_{23} = 8.6$, 2-, 6-H, 4-ClC_6H_4CO); 10.17 (1H, s, NH_{amide}); 10.81 (1H, s, NH_{indole}). Found %: C 63.12; H 4.49; Cl 10.29; N 8.24. $C_{18}H_{15}ClN_2O_3$. Calculated %: C 63.07; H 4.41; Cl 10.34; N 8.17.

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