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SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF (5-AMINO-2-METHYL-1H-INDOL-3-YL)ACETIC ACID

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A method has been developed for obtaining indole compounds containing an amino group in the benzene ring by the indolization of ethyl levulinate p-acetaminophenylhydrazone. A series of derivatives of (5-amino-2-methyl-1H-indol-3-yl)acetic acid at the 5-amino group has been synthesized.

Keywords: (5-amino-2-methyl-1H-indol-3-yl)acetic acid, N-(4-hydrazinophenyl)acetamide, indole, indomethacin, Fischer reaction.

Indomethacin – [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid – is a known anti-inflammatory drugs [1]. The search for biologically active compounds amongst analogs of it is of definite interest. The present work is devoted to the synthesis of indomethacin analogs containing a substituted amino group at position 5 of the benzene ring in place of the methoxyl group, and a free position 1.

One of the known methods of introducing an amino group into the benzene ring of indole compounds is the cyclization of nitrophenylhydrazones of aldehydes and ketones with subsequent reduction of the nitro group [2,3]. The drawback of this method is the low yield of product at the stage of cyclizing nitrophenylhydrazones to indoles. In 1981 Corey and Tramontano, when synthesizing coenzyme PQQ, obtained methyl 6-(formylamino)-5-methoxy-1H-indole-2-carboxylate in 72% yield by the cyclization of methyl 2-{2-[3-(formylamino)-4-methoxyphenylhydrazino}propionate according to Fischer [4]. The results of this work stimulated us to carry out the synthesis of 3-(carboxymethyl)-2-methyl-1H-indole-5-ammonium chloride (**4**) from N-(4-hydrazinophenyl)acetamide.

The distinctive feature of the method developed by us is the use of salt **2** without isolating the free N-(4-hydrazinophenyl)acetamide at the stage of synthesizing the arylhydrazone and Fischer cyclization of the latter without isolation to indole **3**. The yield of compound **3** was 45% calculated on salt **2**. Removal of the N-acetyl protection with simultaneous hydrolysis of the ester was effected with dilute hydrochloric acid giving 3-(carboxymethyl)-2-methyl-1H-indole-5-ammonium chloride **4**. The following were synthesized from compound **4** for biological testing: {5-[(4-chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}acetic acid (**5a**), [5-(acetylamino)-2-methyl-1H-indol-3-yl]acetic acid (**5b**), [5-(benzoylamino)-2-methyl-1H-indol-3-yl]acetic acid (**5c**), {2-methyl-5-[(phenylacetyl)amino]-1H-indolyl-3-yl}acetic acid (**5d**), {5-[(2-hydroxyphenyl)-methyleneamino]-2-methyl-1H-indol-3-yl}acetic acid (**6**), [2-methyl-5-(phenylcarbamoylamino)-1H-indolyl-3-

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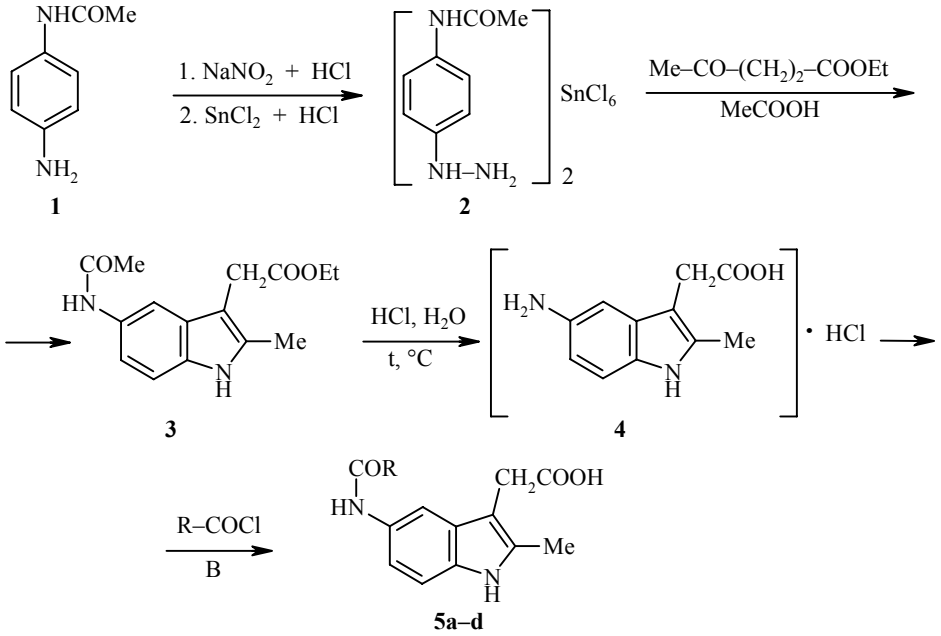
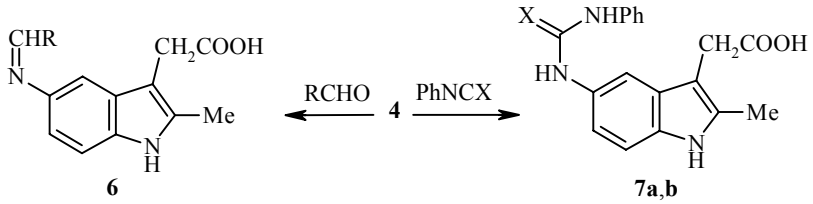
yl]acetic acid (**7a**), and [2-methyl-5-(phenylthiocarbamoylamino)-1H-indol-3-yl]acetic acid (**7b**). The structures of compounds obtained for the first time were established by data of IR and ^{1}H NMR spectroscopy and elemental analysis.



5 a R = *p*-ClC_6H_4; **b** R = Me; **c** R = Ph; **d** R = $PhCH_2$; B = NaOH, triethylamine



6 R = *o*-HOC_6H_4; **7 a** X = O, **b** X = S

EXPERIMENTAL

The IR spectra were taken on a UR 20 instrument in nujol and the ^{1}H NMR spectra on a Bruker WP 200 instrument in the δ scale, internal standard was tetramethylsilane. Analysis by TLC was carried out on Silufol UV 254 plates.

[4-(Acetylamino)phenyl]hydrazine Hexachlorostannate (2). The diazotization of N-(4-aminophenyl)acetamide (**1**) was carried out according to the procedure of [5] with subsequent reduction of the diazonium salt by the addition of a solution of $SnCl_2$ (54.4 g, 0.46 mol) in conc. HCl (50 ml) at -8 to -10°C. The mixture was stirred for 30 min, the precipitated solid was filtered off, and dried in a vacuum desiccator over P_2O_5. Yield 19 g (70%). The product was used without further purification.

Ethyl [5-(Acetylamino)-2-methyl-1H-indol-3-yl]acetate (3). A mixture of salt **2** (14.5 g, 0.07 mol) and ethyl levulinate (10 g, 0.07 mol) in glacial acetic acid (100 ml) was boiled for 1.5 h in a stream of argon. The reaction mixture was poured into water, extracted with ethyl acetate (3×100 ml), the extract was washed with $NaHCO_3$ solution, with water, and dried over Na_2SO_4. The solvent was distilled on a rotary evaporator, and

the residue dried in a vacuum desiccator. Yield 8.85 g (45%); mp 165-167°C. IR spectrum (nujol), ν, cm^{-1}: 1730 (C=O), 3365 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 (3H, t, $CH_2C\underline{H}_3$); 2.01 (3H, s, $COCH_3$); 2.31 (3H, s, CH_3); 3.58 (2H, s, CH_2); 4.03 (2H, m, $C\underline{H}_2CH_3$); 9.68 (1H, s, NH_{amide}); 10.77 (1H, s, NH_{indole}). Found, %: C 65.71; H 6.67; N 10.17. $C_{15}H_{18}N_2O_3$. Calculated, %: C 65.68; H 6.61; N 10.21.

5-Ammonio-3-(carboxymethyl)-2-methyl-1H-indole Chloride (4). A mixture of amide **3** (8.85 g, 0.037 mol) and 18% HCl (30 ml) was boiled for 45 min. The reaction mixture was cooled, the precipitate of crystals was separated, and the filtrate evaporated to dryness on a rotary evaporator. The crystals were washed with ether and dried in a vacuum desiccator over P_2O_5. Yield 6.14 g (84%); mp 215°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 1720 (C=O), 3330 (NH). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, *J* (Hz): 2.43 (3H, s, CH_3); 3.67 (2H, s, CH_2); 7.20 (1H, dd, J_{64} = 1.83, J_{67} = 8.41, $C_{(6)}H$); 7.38 (1H, d, J_{76} = 8.41, $C_{(7)}H$); 7.61 (1H, d, J_{46} = 1.83, $C_{(4)}H$); 11.19 (1H, s, NH); 11.7 (1H, s, COOH). Found, %: C 54.96; H 5.48; Cl 14.62; N 11.59. $C_{11}H_{13}ClN_2O_2$. Calculated, %: C 54.89; H 5.44; Cl 14.73; N 11.64.

{5-[(4-Chlorobenzoyl)amino]-2-methyl-1H-indol-3-yl}acetic Acid (5a). A solution of 4-chlorobenzoyl chloride (1.4 g, 0.008 mol) in chloroform (5 ml) was added dropwise with stirring to a mixture of amine **4** (2 g, 0.008 mol), triethylamine (2.4 g, 0.024 mol), and chloroform (30 ml). The reaction mixture was stirred for 1 h, poured into water, acidified with HCl, and a pasty solid separated. The chloroform layer was separated. The solid was treated with ethanol, and the precipitated crystals filtered off. The filtrate was extracted with ethyl acetate, the ethyl acetate was distilled on a rotary evaporator, and a further quantity of crystals obtained; mp 240-241°C (decomp., from aqueous ethanol). Yield 0.72 g (26%). IR spectrum (nujol), ν, cm^{-1}: 1655 ($C=O_{amide}$), 1715 ($C=O_{acid}$), 3330 (NH_{indole}), 3385 (NH_{amide}). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, *J* (Hz): 2.42 (3H, s, CH_3); 3.66 (2H, s, CH_2); 7.28 (1H, d, J_{76} = 8.56, $C_{(7)}H$); 7.62 (1H, dd, J_{64} = 1.83, J_{67} = 8.56, $C_{(6)}H$); 7.62 (2H, d, J_{32} = 8.40, $C_{(3,5)}H$), 4-ClC_6H_4CO); 7.99 (1H, d, J_{46} = 1.83, $C_{(4)}H$); 8.14 (2H, d, J_{23} = 8.40, $C_{(2,6)}H$, 4-ClC_6H_4CO); 10.23 (1H, s, NH_{amide}); 10.85 (1H, s, NH_{indole}). Found, %: C 63.13; H 4.52; Cl 10.13; N 8.46. $C_{18}H_{15}ClN_2O_3$. Calculated, %: C 63.07; H 4.41; Cl 10.34; N 8.17.

[5-(Acetylamino)-2-methyl-1H-indol-3-yl]acetic Acid (5b) was obtained analogously to **5a** from 5-amino-2-methyl-3-indolylacetic acid hydrochloride (2 g, 0.008 mol) and acetyl chloride (0.63 g, 0.008 mol). The reaction mixture was poured into water, the chloroform layer separated, the aqueous layer was acidified with HCl, extracted with ethyl acetate (3×50 ml), the extract was washed with water, dried over Na_2SO_4, and the solvent distilled on a rotary evaporator. Yield 0.92 g (48%); mp 220-222°C (decomp., from water). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, *J* (Hz): 2.08 (3H, s, $COCH_3$); 2.39 (3H, s, CH_3); 3.61 (2H, s, CH_2); 7.19 (1H, d, J_{76} = 8.77, $C_{(7)}H$); 7.32 (1H, dd, J_{64} = 1.83, J_{67} = 8.77, $C_{(6)}H$); 7.81 (1H, d, J_{46} = 1.83, $C_{(4)}H$); 9.75 (1H, s, NH_{amide}); 10.74 (1H, s, NH_{indole}). Found, %: C 63.49; H 5.61; N 11.51. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.40; H 5.73; N 11.38.

[5-(Benzoylamino)-2-methyl-1H-indol-3-yl]acetic Acid (5c). Benzoyl chloride (1.4 g, 0.01 mol) was added dropwise with stirring and cooling with a water bath to a solution of NaOH (1.04 g, 0.026 mol) and amine **4** (2 g, 0.008 mol) in water (10 ml). The reaction mixture was stirred for 1 h, acidified with HCl, and the precipitated solid was filtered off. Yield 1.6 g (62.5%); mp 129-130°C (decomp., from water). IR spectrum (nujol), ν, cm^{-1}: 1630 ($C=O_{amide}$), 1725 ($C=O_{acid}$), 3400 (NH_{indole}). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, *J* (Hz): 2.41 (3H, s, CH_3); 3.61 (2H, s, CH_2); 7.25 (1H, d, J_{76} = 8.40, $C_{(7)}H$); 7.5 (3H, m, $C_{(3,4,5)}$, C_6H_5CO); 7.54 (1H, dd, J_{64} = 1.83, J_{67} = 8.40, $C_{(6)}H$); 8.00 (1H, d, J_{46} = 1.83, $C_{(4)}H$); 8.11 (2H, d, J_{23} = 8.40, $C_{(2,6)}H$, C_6H_5CO); 10.13 (1H, s, NH_{indole}); 10.76 (1H, s, NH_{amide}). Found, %: C 70.21; H 5.29; N 9.12. $C_{18}H_{16}N_2O_3$. Calculated, %: C 70.12; H 5.23; N 9.09.

{2-Methyl-5-[(phenylacetyl)amino]-1H-indol-3-yl}acetic Acid (5d) was obtained analogously to **5c** from amine **4** (2 g, 0.008 mol), NaOH (1.04 g, 0.026 mol), and phenylacetic acid chloride (1.56 g, 0.01 mol). Yield 0.59 g (22%); mp 208-210°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 1655 ($C=O_{amide}$), 1715 ($C=O_{acid}$), 3300 (NH_{indole}), 3410 (NH_{amide}). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, *J* (Hz): 2.38 (3H, s, CH_3); 3.57 (2H, s,

CH_2); 3.71 (2H, s, C<u>H</u>$_2$CONH); 7.18 (1H, d, J_{76} = 8.41, $C_{(7)}$H); 7.27-7.43 (5H, m, Ph); 7.30 (1H, dd, J_{64} = 1.46, J_{67} = 8.41, $C_{(6)}$H); 7.43 (2H); 7.84 (1H, d, J_{46} = 1.46, $C_{(4)}$H); 10.01 (1H, s, NH_{indole}); 10.72 (1H, s, NH_{amide}). Found, %: C 70.86; H 5.72; N 8.61. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.79; H 5.63; N 8.69.

{[5-(2-Hydroxyphenyl)methyleneamino]-2-methyl-1H-indol-3-yl}acetic Acid (6). A mixture of benzene (30 ml), triethylamine (0.4 g, 0.004 mol), amine **4** (1 g, 0.004 mol), salicylic aldehyde (0.5 g, 0.004 mol), and a few drops of glacial acetic acid was boiled with a Dean–Stark trap for 1 h. The benzene was removed, the residue was treated with water, and the crystals filtered off. Yield 0.5 g (39%). The compound was purified by recrystallization from aqueous ethanol; mp 165°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 1320 (OH), 1650 (C=N), 1725 (C=O), 3400 (NH). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, J (Hz): 2.43 (3H, s, CH_3); 3.69 (2H, s, CH_2); 6.95-7.01 (2H, m, $C_{(4,5)}$, C_6H_4OH); 7.23 (1H, dd, J_{64} = 1.83, J_{67} = 8.77, $C_{(6)}$H); 7.38 (1H, d, J_{76} = 8.77, $C_{(7)}$H); 7.42 (1H, dd, J_{35} = 1.83, J_{34} = 8.77, $C_{(3)}$H, C_6H_4OH); 7.64 (1H, dd, J_{64} = 1.83, J_{65} = 8.77, $C_{(6)}$H, C_6H_4OH); 7.66 (1H, d, J_{46} = 1.83, $C_{(4)}$H); 9.08 (1H, s, CH=N); 11.02 (1H, s, NH). Found, %: C 70.19; H 5.31; N 8.94. $C_{18}H_{16}N_2O_3$. Calculated, %: C 70.12; H 5.23; N 9.09.

[2-Methyl-5-(N-phenylcarbamoylamino)-1H-indol-3-yl]acetic Acid (7a). Phenyl isocyanate (0.48 g, 0.004 mol) was added dropwise with stirring in a stream of argon to a mixture of amine **4** (1 g, 0.004 mol) and absolute DMF (20 ml). The reaction mixture was poured into water, acidified with HCl, and the precipitated crystals were filtered off. Yield 0.35 g (26%). The compound was purified by recrystallization from water; mp 170°C. IR spectrum (nujol), ν, cm^{-1}: 1650 C=O_{amide}), 1705 (C=O_{acid}). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, J (Hz): 2.41 (3H, s, CH_3); 3.59 (2H, s, CH_2); 6.91-7.62 (5H, m, Ph); 7.17 (1H, d, J_{76} = 8.77, $C_{(7)}$H); 7.34 (1H, dd, J_{64} = 1.83, J_{67} = 8.77, $C_{(6)}$H); 7.66 (1H, d, J_{46} = 1.83, $C_{(4)}$H); 9.11 (1H, s, N<u>H</u>CONH); 9.41 (1H, s, NHCON<u>H</u>); 10.62 (1H, s, NH_{indole}). Found, %: C 66.91; H 5.48; N 12.91. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.86; H 5.30; N 13.00.

[2-Methyl-5-(N-phenylthiocarbamoylamino)-1H-indol-3-yl]acetic Acid (7b), was obtained analogously to **7a** from amine **4** (1 g, 0.004 mol) and phenyl isothiocyanate (0.54 g, 0.004 mol). Yield 0.62 g (44%); mp 195-197°C (decomp., from aqueous ethanol). IR spectrum (nujol), ν, cm^{-1}: 1185 (C=S), 1720 (C=O), 3355 (NH_{indole}), 3445 (NH_{amide}). ^{1}H NMR spectrum (DMF-d_7), δ, ppm, J (Hz): 2.41 (3H, s, CH_3); 3.61 (2H, s, CH_2); 7.08-7.69 (5H, m, Ph); 7.13 (1H, dd, J_{64} = 1.46, J_{67} = 8.40, $C_{(6)}$H); 7.25 (1H, d, J_{76} = 8.40, $C_{(7)}$H); 7.49 (1H, d, J_{46} = 1.46, $C_{(4)}$H); 10.08 (2H, s, N<u>H</u>CSN<u>H</u>); 10.84 (1H, s, NH_{indole}). Found, %: C 63.82; H 5.15; N 12.32; S 9.41. $C_{18}H_{17}N_3O_2S$. Calculated, %: C 63.70; H 5.05; N 12.38; S 9.45.

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