γ-METHYLTHIOACETOACETIC ESTER IN THE SYNTHESIS OF 2-INDOLYLACETIC ACID DERIVATIVES

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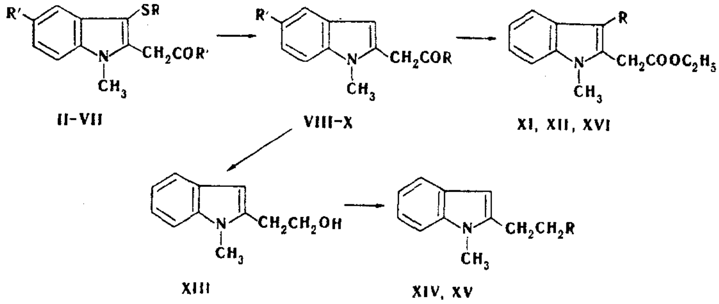
A new method is proposed for the synthesis of 2-indolylacetic acid derivatives with a free β position by condensation of an alkyl-thioacetoacetic ester with arylhydrazines. Some of the reactions of the acids obtained were investigated.

An alkyl(aryl)thioacetoacetic ester (I) has two methylene groups, and Fischer indolization via two pathways to give one of two insomeric indoles or mixtures of them is therefore possible. However, we have shown that indolization in an alcohol solution of formic and sulfuric acids proceeds exclusively in one direction to give 3-alkyl(aryl)thio-2-indolylacetic acid derivatives (II-IV). When the reaction is carried out under more severe conditions – at 180-200°C in polyphosphoric acid (PPA) – a second isomer is also detected chromatographically,* but the reaction is accompanied by pronounced resinification. The frequency of the stretching vibrations of the carbonyl group in the IR spectrum lies in a higher-wavelength region than in the spectrum of the isomeric 1-methyl-2-phenylthiomethyl-3-carbethoxy-5-methoxyindole. As compared with the isomeric compound, which has a conjugated carbonyl group, the absorption maximum in the UV spectrum of IV is shifted by 22 nm to the short-wave region.



II R=CH_3, R′=H, R″=OC_2H_5; III R=C_6H_5, R′=H, R″=OC_2H_5; IV R=C_6H_5, R′=OCH_3, R^2=OC_2H_5; V R=CH_3, R′=H, R^2=OH; VI R=CH_3, R′=H, R″=$NHCH_3$; VII R=CH_3, R′=H, NHC_6H_5; VIII R′=H, R=NHC_6H_5; IX R′=H, R=OC_2H_5; X R′=OCH_3, R=OC_2H_5; XI R=morpholinomethylXII R=piperidinomethyl; XIV R=morpholino; XV R= piperidino

Hydrolysis of ester II with aqueous alcoholic alkali gave acid V, from which amides VI and VII were synthesized through the acid chlorides. In order to obtain 2-indolylacetic acid derivatives with a free β position (IX, X), we carried out the desulfuration of II and IV over a Raney nickel catalyst. A singlet at 6.37 ppm affiliated with the proton in the β position is observed in the PMR spectrum of indole IX. 1-Methyl-2-(2-hydroxyethyl)indole (XIII), obtained by reduction of ester IX, was used for the direct alkylation of the secondary amines in the presence of a Raney nickel catalyst [2], as a result of which we obtained 2-di-

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* 1-Methyl-2-phenylthiomethyl-3-carbethoxy-5-methoxyindole obtained by a different method [1] was used as the reference compound for chromatography.

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TABLE 1. 2-Indolylacetic Acid Derivatives

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
III	101—102	$C_{19}H_{19}NO_2S$	70,1	6,0	4,2	70,1	5,9	4,3	52
IV	133—134	$C_{20}H_{21}NO_3S$	67,8	6,2	3,9	67,6	6,0	3,9	36
VIII	188	$C_{17}H_{16}N_2O$	77,2	6.2	—	77,2	6,1	—	68
X	50—51	$C_{14}H_{17}NO_3$	67,9	6,6	5,5	68,0	6,9	5,7	92
XII	192—193†	$C_{19}H_{27}ClN_2O_2$	65,0	7,9	7,9	65,0	7,8	8,0	57
XV	227—230†	$C_{16}H_{23}ClN_2$	69,0	8,4	—	68,9	8,3	—	80

*The compounds were recrystallized: III, IV, and VIII from alcohol, X from hexane-absolute alcohol, XII from acetone-absolute alcohol, and XV from absolute alcohol.

†The hydrochloride.

alkylaminoethylindole derivatives (XIV, XV). Mannich bases (XII, XIII) were synthesized by aminomethylation of IX. Formylation of IX gave a 3-formylindole derivative (XVI), the IR spectrum of which contains the absorption band of an aldehyde carbonyl group (1655 cm^{-1}).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a C-60 HL spectrometer with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) on aluminum oxide in benzene (II, III, IX) and on Silufol UV-254 plates in chloroform (XVI) and in CCl_4-methanol-triethylamine (20 : 5 : 1) (XI) was used to evaluate the individuality of the compounds obtained.

Ethyl 1-Methyl-3-methylthio-2-indolylacetate (II). A mixture of 3.1 g (0.025 mole) of α-methyl-α-phenylhydrazine and 5.3 g (0.03 mole) of γ-methylthioacetic ester I was heated on a water bath for 2 h, after which the liberated water was removed by vacuum distillation, and a solution of 2.4 ml of sulfuric acid in 24 ml of absolute alcohol was added to the hydrazone formed. After 30 min, the solvent was evaporated, and the resulting precipitate was removed by filtration, washed with aqueous alcohol, and dried to give 2.35 g (35.7%) of ester II with mp 66-67° (from aqueous alcohol) and R_f 0.67. IR spectrum: 1735 cm^{-1} (CO). Found: C 63.8; H 6.4; N 5.3; S 12.0%. $C_{14}H_{17}NO_2S$. Calculated: C 63.8; H 6.5; N 5.3; S 12.2%. Compounds III and IV were similarly obtained (Table 1).

1-Methyl-3-methylthio-2-indolylacetic Acid (V). A mixture of 2.6 (0.01 mole)of ester II and 1 g of sodium hydroxide in 80 ml of alcohol was refluxed for 1 h, after which it was cooled and acidified with dilute formic acid. The resulting precipitate was removed by filtration to give 2.2 g (96%) of acid V with mp 121° (from alcohol). Found: C 61.1; H 5.5%. $C_{12}H_{13}NO_2S$. Calculated: C 61.3; H 5.5%.

N-Methyl-1-methyl-3-methylthio-2-indolylacetamide (VI). A 2.25-g (0.01 mole) sample of phosphorus pentachloride was added to a suspension of 2.35 g (0.01 mole) of acid V in 20 ml of dry ether and 20 ml of acetyl chloride, after which the mixture was refluxed for 1 h and vacuum evaporated. A solution of 0.7 g of methylamine in absolute alcohol was added to the residue, and the mixture was allowed to stand overnight. The precipitated methylamine hydrochloride was removed by filtration, and the filtrate was evaporated to give 0.9 g (36%) of amide VI with mp 139-140° (from aqueous alcohol). Found: C 63.5; H 6.6%. $C_{13}H_{15}N_2OS$. Calculated: C 63.0; H 6.5%.

N-Phenyl-1-methyl-3-methylthio-2-indolylacetamide (VII). A solution of 0.45 g (0.0035 mole) of phosphorus trichloride in 5 ml of benzene was added dropwise to a mixture of 2.11 g (0.009 mole) of acid V and 0.86 g (0.009 mole) of aniline in 150 ml of dry benzene, after which the mixture was refluxed for 3 h. It was then washed successively with sodium carbonate solution and water and vacuum evaporated. The residue was recrystallized from alcohol to give 2.2 g (77.7%) of amide VII with mp 195°. Found: C 69.6; H 6.0; N 9.2%. $C_{18}H_{18}N_2OS$. Calculated: C 69.6; H 5.8; N 9.0%.

Ethyl-1-Methyl-2-indolylacetate (IX). A solution of 1.8 g (0.007 mole) of II in 20 ml of dioxane was refluxed for 6 h with 10 g of Raney nickel catalyst, after which it was cooled, and the catalyst was removed by filtration and washed on the filter several times with hot dioxane. The solvent was evaporated, and the residue was separated, washed with aqueous alcohol, and dried to give 1.4 g (92%) of ester IX with mp 49° (from hexane) and R_f 0.74. IR spectrum: 1745 cm^{-1} (CO). UV spectrum, λ_{max}, nm (log ε): 224 (4.56) and 284 (3.90). PMR spectrum (δ, ppm, singlet): 3.64 ($N-CH_3$), 3.75 ($-CH_2-$), and 6.37 (3-H). Found:

C 72.0; H 7.0; N 6.1%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 7.0; N 6.5%. Compounds X and VIII were similarly obtained (see Table 1).

1-Methyl-2-(2-hydroxyethyl)indole (XIII). A solution of 2.17 g (10 mmole) of IX in 20 ml of dry ether was added dropwise to a suspension of 2 g of lithium aluminum hydride in 80 ml of dry ether, after which the mixture was refluxed for 6 h. It was then cooled and treated with 2 ml of water, and the ether layer was separated. The residue was washed twice with ether, and the combined extracts were dried with magnesium sulfate and evaporated to give 1.15 g (59%) of alcohol XIII with mp 58-60° (from petroleum ether). Found: C 75.4; H 7.4%. $C_{11}H_{13}NO$. Calculated: C 75.4; H 7.5%.

1-Methyl-2-(2-N-morpholinoethyl)indole (XIV) Hydrochloride. A mixture of 1.25 g (0.0075 mole) of XIII, 0.65 g (0.0075 mole) of morpholine, 0.5 ml of a suspension of a Raney nickel catalyst in water, and 10 ml of benzene was refluxed for 4 h with removal of the water by azeotropic distillation. The hot solution was filtered, the catalyst was washed several times with hot benzene, and the combined filtrates were evaporated to dryness. The residue was dissolved in absolute alcohol, and XIV was isolated as the hydrochloride. The yield of hydrochloride with mp 205-207° (from absolute alcohol) was 1.2 g (66%). Found: C 64.3; H 7.7; N 9.8%. $C_{15}H_{21}ClN_2O$. Calculated: C 64.2; H 7.5; N 10.0%. The hydrochloride of XV was similarly obtained (Table 1).

Ethyl 1-Methyl-3-morpholinomethyl-2-indolylacetate (XI). A solution of 1.95 g (0.009 mole) of IX in 3 ml of dioxane was added to a mixture of 0.87 g (0.01 mole) of morpholine, 1.5 ml of acetic acid, and 1 ml of 40% formalin solution, after which the mixture was allowed to stand at room temperature for 24 h. The dioxane was then vacuum evaporated, and the residue was diluted with water and made alkaline with 10% sodium hydroxide solution. The resulting precipitate was evaporated, washed with water, and dried to give 2.2 g (80%) of amine XI with mp 96-97° (from hexane) and R_f 0.76. Found: C 68.1; H 7.7; N 8.9%. $C_{18}H_{24}N_2O_3$. Calculated: C 68.3; H 7.7; N 8.9%. Compound XII was similarly obtained (Table 1).

Ethyl 1-Methyl-3-formyl-2-indolylacetate (XVI). A solution of 2.17 g (0.01 mole) of IX in 4 ml of dimethylformamide (DMF) was added dropwise in the course of 30 min to a mixture of 1.6 g (0.0115 mole) of phosphorus trichloride and 25 ml of DMF, after which the mixture was heated on a water bath at 55-60° for 30 min. It was then cooled, and 10 g of crushed ice and 10 ml of cold water were added carefully. A solution of 2 g of sodium hydroxide in 10 ml of water was then added dropwise with stirring, after which the mixture was diluted with water and allowed to stand overnight. The resulting precipitate was removed by filtration, washed with water, and dried. The yield of XVI, with mp 115° (from petroelum ether), was 1.8 g (77%). IR spectrum: 1735 and 1655 cm^{-1} (CO). Found: C 68.1; H 6.3%. $C_{14}H_{15}NO_3$. Calculated: C 68.4; H 6.2%.

LITERATURE CITED

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