3-(1-Methyl-5-phenyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XVII). A mixture of 1.7 g (8 mmole) of alcohol X was stirred thoroughly with 2 g (12 mmole) of N-methylphenylcarbamoyl chloride, after which the mixture was heated at 110-120° for 4 h. It was then cooled, and the resulting viscous oil was triturated with ether to isolate crystals of salt XVII with mp 110° in 50% yield. Found, %: Cl 9.2; N 6.7. $C_{22}H_{28}N_2O_2 \cdot HCl$. Calculated, %: Cl 9.4; N 7.2.

3-(1-Methyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XVIII). This compound, with mp 113-115°, was similarly obtained in 80% yield from alcohol XI. Found, %: Cl 10.4. N 8.9. $C_{16}H_{24}N_2O_2 \cdot HCl$. Calculated, %: Cl 10.1; N 8.9.

3-(1-Methyl-5-isobutyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XIX). This compound, with mp 97-98°, was similarly obtained in 70% yield from alcohol XII. Found, %: Cl 9.2; N 7.4. $C_{20}H_{32}N_2O_2 \cdot HCl$. Calculated, %: Cl 9.6; N 7.6.

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SYNTHESIS OF N-SUBSTITUTED INDOLES BY EXTRACTIVE ALKYLATION

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UDC 547.753.07:542.953

A method was developed for the N-alkylation of indole and its derivatives by alkyl halides in the presence of sodium hydroxide and catalytic amounts of trimethylbenzylammonium chloride.

N-Alkylindoles are used for the preparation of indomethacin analogs that have antiphlogistic activity [1, 2], and also in diverse syntheses in the indole series.

The alkylation of indole itself is realized through its metallated derivatives. The natures of the metal and the solvent have the greatest effect on the direction of alkylation (at N or in the 3 position). An increase in the ionic character of the nitrogen—metal bond by utilization of alkali metals (Na and K) [3] and strongly dissociating solvents [dimethyl

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*The authors thank Prof. A. N. Kost for his critical remarks and advice during a discussion of the results of our research on the alkylation of N-carbomethoxy-3-indolylcyanoacetic ester

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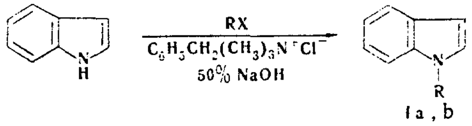
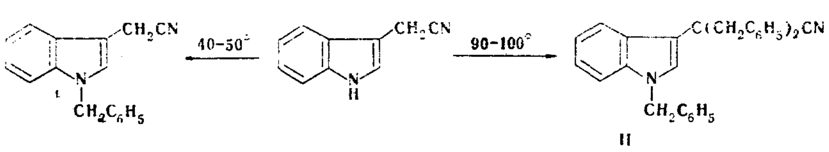
sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPT)] [4, 5] favors N-alkylation.

An analysis of the literature data makes it possible to assume that the method of extractive alkylation [6] should lead to primary N-alkylation because of the purely ionic character of the indole nitrogen atom–ammonium bond. In fact, we obtained N-alkylindoles Ia,b in high yields by reaction of indole with halo derivatives (ethyl bromide and benzyl chloride) under these conditions.

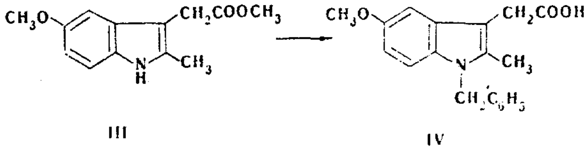


Ia R = C_2H_5; b R = $C_6H_5CH_2$; X = halogen

The simplicity of the reaction makes it possible to recommend it for the preparation of N-alkylindoles. Our method differs favorably from the known methods in that it is realized without the use of reagents such as sodium amide and sodium hydride and large amounts of aprotic dipolar solvents. This method may be used for the N-alkylation of 3-substituted indoles, and exclusively N-alkylation may also be achieved when an activated methylene group is present in the molecule. Thus, for example, 3-indolylacetic acid and its nitrile are easily N-benzylated. In the latter case the reaction temperature is of importance — only N-alkylation is observed at 40-50°, whereas at higher temperatures (80-90°) the product of N- and C-alkylation — N,α,α-tribenzyl-3-indolylacetonitrile (II) — is formed.



The presence of a substituent in the 2 position does not interfere with N-alkylation. Thus, N-benzyl-2-methyl-5-methoxy-3-indolylacetic acid (IV) was obtained in the benzylation of methyl 5-methoxy-2-methyl-3-indolylacetate (III).



EXPERIMENTAL

N-Benzylindole. An 11.7-g (0.10 mole) sample of indole and 40 ml of 50% NaOH were added to a mixture of 15.2 g (0.12 mole) of benzyl chloride and 0.2 g of trimethylbenzylammonium chloride, after which the mixture was stirred at 60-70° for 5 h. It was then diluted with three 100-ml portions of ether. The ether extracts were washed with water and dried over anhydrous $MgSO_4$, and the ether was removed by distillation to give 19.2 g of an oil which crystallized on standing to give a product with mp 43-44° (mp 43-45° [5]) in 96% yield.

N-Ethylindole. This compound was similarly obtained from 3 g of indole and 5 g of ethyl bromide in 20 ml of 50% NaOH solution in the presence of catalytic amounts of trimethylbenzylammonium chloride. The yield of product with n_D^{20} 1.5885 and bp 108-109° (3 mm) [bp 83-86° (0.6 mm) [4]] was 2.8 g.

N-Benzyl-3-indolylacetonitrile. A mixture of 2 g (0.0125 mole) of 3-indolylacetonitrile, 0.2 g of trimethylbenzylammonium chloride, 3 g (0.025 mole) of benzyl chloride, and 20 ml of 50% NaOH was stirred at 40-50° for 4 h, after which the precipitate was removed by filtration and washed with water, alcohol, and ether to give 3 g (97.5%) of a product with mp 95-96° (from alcohol). Found, %: C 82.6; H 5.8; N 11.4. $C_{17}H_{14}N_2$. Calculated, %: C 82.9; H 5.7; N 11.4. The IR spectrum of the product did not contain the absorption band of an indole NH group.

N,α,α-Tribenzyl-3-indolylacetonitrile. A mixture of 2 g (0.0125 mole) of 3-indolylacetonitrile, 0.2 g of trimethylbenzylammonium chloride, 5 g (0.042 mole) of benzyl chloride, and 20 ml of 50% NaOH solution was stirred at 90-100° for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water, alcohol, and ether to give 1.2 g (23%) of a product with mp 164-165°. Found, %: C 87.2; H 6.1; N 6.4. $C_{31}H_{26}N_2$. Calculated, %: C 87.3; H 6.1; N 6.6.

N-Benzyl-3-indolylacetic Acid. A mixture of 0.87 g (0.005 mole) of 3-indolylacetic acid, 1.5 g (0.012 mole) of benzyl chloride, and 0.02 g of trimethylbenzylammonium chloride was dissolved at 60°, after which 2 ml of 50% NaOH solution was added, and the mixture was stirred at 65-70° for 6 h. It was then cooled and extracted with ether, and the aqueous layer was acidified with 10% HCl and extracted several times with ether and ethyl acetate. The combined extracts were washed with water and dried over anhydrous $MgSO_4$, and the solvent was removed by distillation to give 1 g (80%) of an oil which crystallized on standing to give a product with mp 149-150° (mp 148° [7]).

N-Benzyl-2-methyl-5-methoxy-3-indolylacetic Acid. A 1.08-g (0.0046 mole) sample of methyl 2-methyl-5-methoxy-3-indolylacetate was dissolved in 1.5 g (0.012 mole) of benzyl chloride at 60-70°, after which 2 ml of 50% NaOH and 0.2 g of trimethylbenzylammonium chloride were added, and the mixture was stirred at 70° for 5 h. It was then cooled and extracted with ether, and the aqueous layer was acidified with 10% HCl and extracted with ethyl acetate. The ethyl acetate extracts were dried over anhydrous $MgSO_4$, and the solvent was removed by distillation to give 0.8 g (57%) of an oil which crystallized on standing to give a product with mp 174-175° (from alcohol). Found, %: C 73.6; H 6.0; N 4.5. $C_{19}H_9NO_3$. Calculated, %: C 73.8; H 6.2; N 4.5.

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