INTRODUCTION OF 3-INDOLYLMETHYL RESIDUES IN NITROACETIC ACID ESTERS

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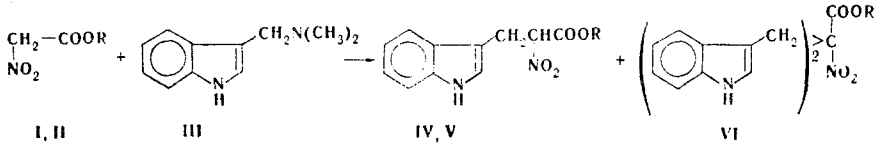
A method for the monoalkylation of nitroacetic ester with gramine in the presence of triethylamine is proposed. The basis of the method is the difference in the acidity of the nitroacetic acid ester and its monoalkylation product. The synthesis of β-(3-indolyl)-β-R-α-nitropropionic acid esters (R = Me, Ph), which are precursors of β-substituted tryptophans, was accomplished for the first time by alkylation of nitroacetic ester with indole Mannich bases containing alkyl or aryl substituents in the methylene group.

The alkylation of methyl and ethyl nitroacetates (I and II) with gramine (III) in order to obtain β-(3-indolyl)-α-nitropropionic acid esters (IV and V), which are precursors of tryptophan, is accompanied by the formation of dialkylation products (VI) [1].



I, II III IV, V VI

I, IV, VI R = C_2H_5; II, V R = CH_3

Weisblat and Lyttle [2] used a twofold excess of nitroacetic ester to suppress this undesired process. Largman [3] carried out alkylation in two stages: a) prior preparation and isolation of the salt of the nitroacetic acid ester with gramine and b) the alkylation itself.

To achieve the same result we attempted to use known methods for the monoalkylation of nitroalkanes with gramine N-oxide [4] or gramine in the presence of a quaternizing agent — dimethyl sulfate and sodium ethoxide (the Heath-Brown—Philpott method) — in the presence of excess nitroalkane in both cases.

We have established that although only monoalkylation of nitroacetic acid ester I (to give ester IV) takes place in the case of the Heath-Brown—Philpott method [5], this method does not have any advantages over the Weisblat—Lyttle method [2], since ester IV is obtained in 60% yield only in the case of a threefold excess of starting ester I. Mono- and dialkylation products IV and VI are obtained in 45 and 18% yields, respectively, in the case of an equimolar reagent ratio. In this case a significant amount of the gramine is consumed in the formation of ethoxymethylindole (in 37% yield), which is inert with respect to the nitroacetic acid ester.

Alkylation of nitroacetic acid ester I with gramine N-oxide by the method in [4] gave monoalkylation product IV (10%) in addition to numerous side products, among which O-indolylmethylhydroxylamine — the result of rearrangement of gramine N-oxide — was identified. Alkylation of an equimolar amount of nitroacetic acid ester I with gramine N-oxide in the presence of KF in dimethyl sulfoxide (DMSO) gives exclusively dialkylation product VI, which was isolated in 60% yield in the form of a complex with CCl_4.

We also established that in the synthesis of esters IV and V from the gramine salts [3] of methyl and ethyl esters I and II obtained in situ (without prior isolation) a satisfactory yield (81%) is obtained only in the case of the methyl ester (the yield is only 67% in the case of the ethyl ester); ester IV can be obtained in 90% yield when the previously isolated salt of ethyl nitroacetate and gramine [3] is used.

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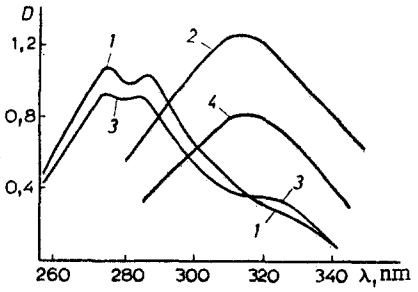


Fig. 1. UV spectra of esters I and IV ($c = 1 \cdot 10^{-4}$ M in ethanol): 1) IV, $c_{(C_2H_5)_3N} = 0.1$ M; 2) I, $c_{(C_2H_5)_3N} = 0.1$ M; 3) IV, $c_{NaOH} = 1 \cdot 10^{-4}$ M; 4) I, $c_{NaOH} = 1 \cdot 10^{-4}$ M.

We propose a new method [6] for the alkylation of an equimolar amount of ester I with gramine in which the reaction is carried out in toluene in the presence of triethylamine, and IV is obtained in 90% yield. The method is characterized by the fact that, in contrast to the method in [2], it does not require excess ester I and by the fact that, in contrast to the method in [3], it makes it possible to carry out the process in one step.

The basis of the proposed method is the difference in the acidities of starting ester I and monoalkylation product IV. The pK_a values of I and IV are, respectively, 5.8 [7] and 6.9 (by potentiometry) in water and 12 and 13.9 (by spectrophotometry) in alcohol. Since the anion of the nitro compound participates in the alkylation [8], the use of weak bases of the triethylamine type should favor the formation of an anion only from ester I and, consequently, the formation of monoalkylation product IV.

In fact, a study of the UV spectra of alcohol solutions of esters I and IV showed that in the presence of a weak base — triethylamine — ester IV gives virtually no anionic form even in the case of a large excess of base, whereas ester I gives significant amounts of the anionic form (Fig. 1).

We also established that a variant involving alkylation in pyridine, which acts both as the solvent and a weak base, is a method that is comparable with respect to its results to alkylation in the presence of triethylamine. Monoalkylation products IV and V are obtained in 79-81% yields in this case.

According to the data from the UV spectra of esters I and IV in an alcohol solution of sodium ethoxide, both esters form considerable amounts of the anionic forms even in the presence of an equimolar amount of base (Fig. 1).

In agreement with this, the use of strong bases — secondary amines, Na_2CO_3, NaOH, and sodium ethoxide — makes dialkylation of nitroacetic acid ester the dominant reaction, and the yield of monoalkylation product decreases from 60-65% to 32%. The structure of the secondary amine introduced in the reaction (diethyl-, dibutyl-, and dioctadecylamines) does not have a substantial effect on the ratio of the yields of the alkylation products (mono:di ≈65:35%).

This result is in agreement with the data in [9, 10] regarding suppression of the dialkylation of cyanoacetic and malonic esters in the presence of weak bases.

We established that the monoalkylation products are expediently separated from the dialkylation products in the form of ammonium salts obtained by the action of gaseous ammonia.

The preparation of monoalkylation products in the form of ammonium salts is also expedient because of the fact that tryptophan and its derivatives can be obtained directly from them. The catalytic hydrogenation of these salts proceeds under the same conditions as the hydrogenation of the nitro esters (IV and V) — in the presence of 5% $Pd/CaCO_3$ of W-4 Raney nickel in ethanol at atmospheric hydrogen pressure [11].

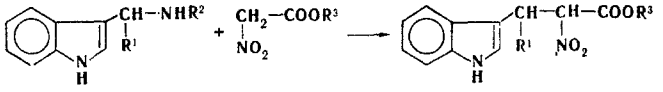
We also used nitroacetic acid esters I and II in the synthesis of methylene-substituted esters of β-(3-indolyl)-α-nitropropionic acid (VII-IX), which are intermediates in the synthesis of β-substituted tryptophans. This method was used to obtain β-methyltryptophan, which, according to the data in [12], activates the enzyme synthesis of L-tryptophan and is

TABLE 1. Ethyl β-(3-Indolyl)-β-R^1-α-nitropropionates and N-Acetyl-β-R^1-tryptophans

Compound	R^1	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
VII	CH_3	112—114[a]	61,0	5,7	10,1	$C_{14}H_{16}N_2O_4$	61,0	5,8	10,1	80
VIII	C_6H_5[b]	146—147[c]	66,7	5,1	8,6	$C_{18}H_{16}N_2O_4$	66,7	5,0	8,6	80
IX	C_6H_5	78—83	67,8	5,2	8,1	$C_{19}H_{18}N_2O_4$	67,5	5,3	8,3	86
XII	CH_3	136—140	66,3	6,8	9,9	$C_{16}H_{20}N_2O_3$	66,6	7,0	9,7	91
XIII	C_6H_5	175—178	71,9	6,3	8,0	$C_{21}H_{22}N_2O_3$	72,0	6,3	8,0	96

a) Softens at 80-85°C. b) Methyl ester. c) Softens at 120-125°C.

incorporated in the composition of the peptide antibiotic telomycin [13]. β-Methyltryptophan was previously obtained by a multistep synthesis from dibenzyl acetamidomalonate [14].



X, XI I, II VII-IX

X $R^1=CH_3$, $R^2=H$; XI $R^1=C_6H_5$, $R^2=CH_3$; VII $R^3=C_2H_5$; VIII $R^3=CH_3$; IX $R^3=C_2H_5$

We used primary and secondary amines (X and XI) (Mannich bases) to introduce 3-indolylmethyl groups containing alkyl and aryl substituents in the methylene group in nitroacetic acid esters I and II. Amines X and XI are easily obtained by known methods [15, 16] and react readily with esters I and II when the components are heated in toluene. Substituted β-indolyl nitro esters VII-IX are formed in high yields without any complications due to the formation of side compounds. The hydrogenation of VII-IX was carried out under the conditions used for the hydrogenation of esters IV and V. dl-Tryptophan, dl-N-acetyltryptophan, and racemic β-methyltryptophan were obtained by standard methods of hydrolysis of acetamido esters.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of the compounds were recorded with an SFT-20 spectrometer (80 MHz). The UV spectra were recorded with a Specord spectrophotometer.

Mannich Bases. Pure-grade gramine was used without additional purification. 3-(1-Aminoethyl)indole was obtained by the method in [15], and 3-(1-methylaminobenzyl)indole was obtained by the method in [16].

General Method for the Preparation of β-(3-Indolyl)-α-nitropropionic Acid Esters (IV and V). A 10-mmole sample of nitroacetic acid ester I or II was added with stirring in a stream of an inert gas to a suspension of 10 mmole of the Mannich base (III, X, or XI) in 25 ml of dry toluene.* After 45 min, another 75 ml of toluene was added, and the mixture was heated with vigorous stirring at 95-105°C in a stream of an inert gas until the liberation of amine ceased (10-12 h). The mixture was then washed successively with 5% HCl solution and water to neutrality, and the toluene solution was dried with $MgSO_4$ and evaporated. The crude oily residue was recrystallized (or reprecipitated) from chloroform—hexane or, in the case of gramine, dry ammonia was bubbled through a toluene or ether solution of the crude product until precipitation ceased. The ammonium salt was removed by filtration and washed with toluene or ether. Toluene or ether was added to the salt, and the mixture was treated with 10% aqueous HCl solution. The aqueous layer was separated, washed with water, and dried with $MgSO_4$. The solvent was removed by evaporation, and the residue was crystallized from chloroform—petroleum ether to give methyl β-(3-indolyl)-α-nitropropionate (V) (in 81% yield), with mp 60-61°C (mp 44-46°C [17]), or ethyl β-(3-indolyl)-α-nitropropionate (IV) (in 90% yield), with mp 61-62°C (mp 60-62°C [2]). The yields and melting points of β-R^1-nitro esters VII-IX are presented in Table 1.

*The alkylation of ester L with gramine was carried out in the presence of an equimolar amount of triethylamine.

TABLE 2. PMR Spectra of β-(3-Indolyl)-β-R^1-α-nitropropionic Acid Esters in CD_3OD

Compound	R^1	R^3	Chemical shifts, ppm, and multiplicities				
			α-H	β-H	R^1	R^3	
						CH_3	CH_2
VII	CH_3	C_2H_5	5,53 d 5,44 d	4,00 m 3,95 m	1,50 d 1,51 d	0,80 t 1,23 t	3,83 q 4,18 q
VIII	C_6H_5	CH_3	5,11 d 4,96 d	5,85 d[a] 6,00 d[a]	6,75—7,42m	3,22 s 3,26 s	—
IX	C_6H_5	C_2H_5	5,22 d 5,31 d	6,12 d[a] 6,27 d[a]	6,95—7,79 m	0,87 t[b]	3,87 q[b]

a) Splitting of the aromatic protons (J ≈ 0.1-0.2 Hz). b) double set of signals.

Ethyl β,β-Di(3-indolyl)-α-nitroisobutyrate (VI). A 0.75-g (13 mmole) sample of anhydrous KF, 10-15 ml of DMSO, and 1.12 g (5 mmole) of crystalline gramine N-oxide [4] were added to 0.6 g (4.5 mmole) of nitroacetic acid ester, and the mixture was stirred for 2 h, after which it was poured into 200 ml of cold (5-7°C) water, and the aqueous mixture was extracted with toluene. The extract was washed successively with 5% NaOH and water (to neutrality) and dried with $MgSO_4$. The solvent was removed from the extract by evaporation, and the oily residue was crystallized from CCl_4 to give 0.52 g (60% based on gramine N-oxide) of a product with mp 94-96°C. Found: C 52.2; H 4.0; N 7.9%. $C_{22}H_{21}N_3O_4 \cdot CCl_4$. Calculated: C 51.9; H 3.9; N 7.9%. IR spectrum: 1555 (NO_2); 1725 ($CO_2C_2H_5$); 3420, 3460 cm^{-1} (NH).

General Method for the Preparation of N-Acetyl Derivatives and Hydrochlorides of Tryptophan and β-R^1-Tryptophan Esters. A suspension of 4-5 g of W-4 Raney nickel in 100 ml of ethanol was placed in a hydrogenation flask equipped with a thermostatted jacket, 1 g of nitro ester (IV, V, VII-IX) or its ammonium salt (in the case of IV and V) was added, and hydrogenation was carried out at atmospheric pressure until hydrogen absorption ceased. The reaction mixture was filtered, and the filtrate was evaporated. The hydrochloride of the tryptophan ester can be isolated by two methods: a) finely crushed ice and 5 ml of 10% aqueous HCl solution were added successively to the residue, and the precipitated salt was removed by filtration; b) the residue was treated with 15 ml of a 5% solution of HCl in absolute ethanol, after which 200 ml of absolute ether was added at 0-5°C, and the resulting precipitate was removed by filtration, dried, and crystallized. These procedures were used to obtain tryptophan ethyl ester hydrochloride (in 84% yield), with mp 225-227°C (from ethanol), and tryptophan methyl ester hydrochloride (in 85% yield; in 79% yield in the case of hydrogenation of the ammonium salt) with mp 228°C (dec., from methanol). No melting-point depressions were observed for mixtures of the products with authentic samples.

To obtain the N-acetyl derivative the evaporated filtrate containing the tryptophan ester was treated with acetic anhydride, and the mixture was dissolved in absolute ether (toluene). After 24 h, the solution was filtered, and the filtrate was vacuum evaporated at 60-70°C. The residue from the evaporation crystallized rapidly. N-Acetyltryptophan ethyl was obtained in 88% yield and had mp 129-130°C (mp 130-133°C [18]). N-Acetyl-β-R^1-tryptophan esters (XII and XIII) were similarly obtained (the yields and melting points are presented in Table 1).

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TRANSFORMATIONS OF PYRROLANTHRONE-1-CARBOXYLIC ACID

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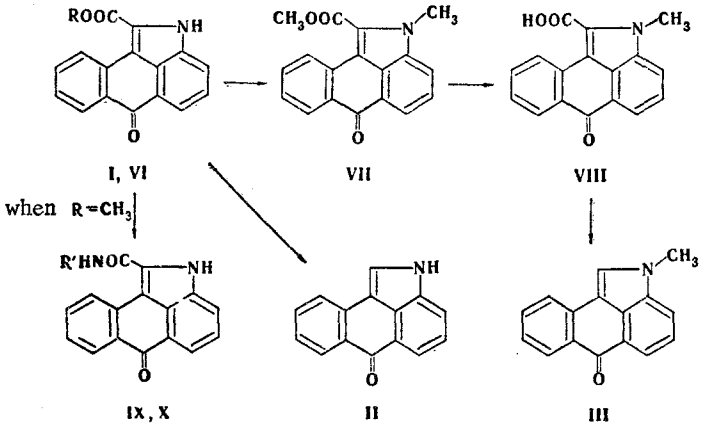
The preparative possibilities of syntheses based on pyrrolanthrone-1-carboxylic acid were studied. Methylation of the acid or its ester leads to N-methylpyrrolanthrone-1-carboxylic acid esters. The esters were converted to amides and hydrazides, and the latter were converted to 1-amino derivatives through the azides. The indicated transformations and decarboxylation in phosphoric acid give the products in high yields.

In a previous communication [1] we described the contraction of the heteroring in 1-diazoanthrapyridone to give pyrrolanthrone-1-carboxylic acid (I) and its esters. This transformation is the first preparative method for the synthesis of derivatives of pyrrolanthrone (6H-naphth[1,2,3-cd]indol-6-one), a heterocyclic polycondensed system that was previously difficult to obtain and has not been adequately studied. The present paper is devoted to a study of the transformations of the carboxyl group in the hope of obtaining key compounds for further syntheses — pyrrolanthrone (II), N-methylpyrrolanthrone (III), and their 1-amino derivatives (IV and V).

The action of various methylating agents (methyl iodide, diazomethane, and dimethyl sulfate) in alkaline media on acid I or its methyl ester (VI) leads to the same product — methyl N-methylpyrrolanthrone-1-carboxylate (VII), the hydrolysis of which gave the corresponding acid (VIII). Acids I and VIII, in contrast to pyrrolecarboxylic acids [2], are not capable



I R=H; VI R=CH_3; IX R'=H; X R=n-C_4H_9

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