INDOLIZINES

III.* SOME ELECTROPHILIC SUBSTITUTION REACTIONS IN THE 2-METHYL(ARYL)-7-ETHOXYCARBONYLINDOLIZINE SERIES

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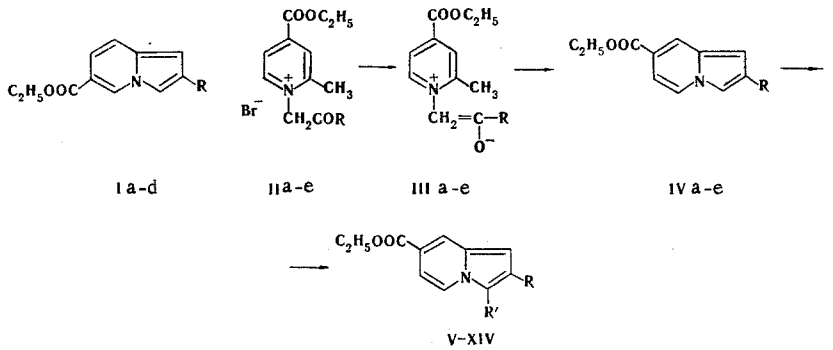
A comparative study was made of electrophilic substitution reactions of isomeric 2-methyl(aryl)-7-ethoxycarbonyl- and 2-methyl(aryl)-6-ethoxycarbonylindolizines, and it was shown that 6-ethoxycarbonylindolizines have higher reactivities.

In order to make a comparative study of the electrophilic substitution of two isomeric series – 2-methyl-(aryl)-6-ethoxycarbonylindolizines I and 2-methyl(aryl)-7-ethoxycarbonylindolizines (IV) – we additionally obtained some new 2,7-disubstituted indolizines (IVc-e) via the scheme described in [2].



I a-d II a-e III a-e IV a-e V-XIV

I, II, III, IV a R=CH_3; b R=C_6H_5; c R=*p*-$C_6H_4OCH_3$; d R=*p*-$C_6H_4NO_2$; e R=*p*-C_6H_4Br

Anhydro bases IIIc-e, which were isolated from 1-phenacyl-2-methyl-4-ethoxycarbonylpyridinium bromides IIc, e and were previously described in [2], proved to be considerably more stable compounds than the isomeric 1-phenacyl-2-methyl-5-ethoxycarbonylpyridinium anhydro bases. In contrast to the latter, which undergoes cyclization at an appreciable rate even at room temperature [1], anhydro bases IIIb-e can be stored for a long time without undergoing apparent conversion to indolizines. The 2-substituted 7-ethoxycarbonylindolizines (IVa-e) proved to be considerably less reactive than indolizines I. This was demonstrated in the case of acylation, Vilsmeier, and Mannich reactions. Thus the reaction of indolizines IVb,c with acetic anhydride is complete only after prolonged (20-40 h) refluxing, and the corresponding indolizines Ib,c are acetylated after 10 h. The decrease in the reactivities of the indolizines when the ethoxycarbonyl group is transferred from the 6 position to the 7 position of the two-ring compounds shows up even more clearly in the acylation of the 2-methyl derivatives (Ia and IVa). Whereas the reaction of IVa with acetic anhydride and benzoyl chloride proceeds smoothly when the reagents are heated, under similar conditions indolizine Ia reacts violently with resinification of the reaction products, and the desired compounds were not isolated when this method was used. Only benzoylation of Ia at room temperature in the presence of triethylamine made it pos-

*See [1] for communication II.

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sible to obtain 2-methyl-3-benzoyl-6-ethoxycarbonylindolizine [1]. The Vilsmeier formylation of indolizines Ia and IVa is also illustrative. Monoformyl derivative VI is formed under the same conditions from IVa, whereas a 1,3-diformyl derivative is obtained from Ia. The Mannich dimethylaminomethylation of indolizines I proceeds even more readily, and mainly 1,3-bis(dimethylaminomethyl) derivatives are formed in this case [1]. At the same time, only a monosubstitution product (XIII) was obtained in the Mannich reaction from 2-phenyl-7-ethoxycarbonylindolizine (IVb).

The decrease in the reactivities of 7-ethoxycarbonylindolizines with respect to electrophilic reagents as compared with 6-ethoxycarbonylindolizines is evidently associated with the large acceptor effect of the ester group attached to $C_{(7)}$ in the para position to the nitrogen atom on the decrease in the electron density on the $C_{(1)}$ and $C_{(3)}$ atoms of the pyrrole fragment as compared with the meta effect of an ethoxycarbonyl group with respect to the nitrogen atom of 6-ethoxycarbonylindolizines. The electron-donor methyl group attached to $C_{(2)}$ to a certain degree compensates the effect of the ester group, and 2-methylindolizines are more reactive than 2-arylindolizines. On the other hand, the introduction in the para position of the aryl substituent attached to $C_{(2)}$ of a halo or nitro group appreciably reduces the electron density on the $C_{(1)}$ and $C_{(3)}$ atoms, and indolizine Id behaves like 2-aryl-7-ethoxycarbonylindolizines in electrophilic substitution reactions.

EXPERIMENTAL

The synthesis of II-IVa,b was described in [2].

1-(p-Methoxyphenacyl)-2-methyl-4-ethoxycarbonylpyridinium Bromide (IIc). A solution of 2.4 g (14.5 mmole) of 2-methyl-4-ethoxycarbonylpyridine and 3.3 g (14.5 mmole) of p-methoxyphenacyl bromide in 7 ml of acetone was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration and washed with acetone to give 4.9 g (86%) of a product with mp 160-161° (from ethanol). Found: Br 20.2%. $C_{18}H_{20}BrNO_4 \cdot H_2O$. Calculated: Br 20.3%. Compounds IId, e were similarly obtained.

1-(p-Nitrophenacyl)-2-methyl-4-ethoxycarbonylpyridinium Bromide (IId). This compound, with mp 148-150° (dec., from ethanol), was obtained in 64.6% yield. Found: Br 19.8%. $C_{17}H_{17}BrN_2O_5$. Calculated: Br 19.5%.

1-(p-Bromophenacyl)-2-methyl-4-ethoxycarbonylpyridinium Bromide (IIe). This compound, with mp 190-192° [dec., from ethanol–acetone], was obtained in 60% yield. Found: Br 36.3%. $C_{17}H_{17}Br_2NO_3$. Calculated: Br 36.1%.

1-(p-Methoxyphenacyl)-2-methyl-4-ethoxycarbonylpyridinium Anhydro Base (IIIc). A total of 16 ml of 25% ammonium hydroxide was added with cooling to a solution of 8.2 g (21 mmole) of IIc in 130 ml of water, and the mixture was allowed to stand for 30 min. Bright-orange precipitate was removed by filtration, washed with water, and dried to give 6.5 g (100%) of a product with mp 101-103°. Found: C 68.8; H 6.0%. $C_{18}H_{19}NO_4$. Calculated: C 69.0; H 6.1%.

1-(p-Nitrophenacyl)-2-methyl-4-ethoxycarbonylpyridinium Anhydro Base (IIId). This compound, with mp 166-168°, was obtained in 93.6% yield. Found: C 62.0; H 4.9; N 8.4%. $C_{17}H_{16}N_2O_5$. Calculated: C 62.2; H 4.9; N 8.5%.

1-(p-Bromophenacyl)-2-methyl-4-ethoxycarbonylpyridinium Anhydro Base (IIIe). This compound, with mp 103-104°, was obtained in 95.5% yield. Found: C 56.2; H 4.5; Br 22.3%. $C_{17}H_{16}BrNO_3$. Calculated: C 56.4; H 4.6; Br 22.1%.

2-(p-Methoxyphenyl)-7-ethoxycarbonylindolizine (IVc). A 13.4-g (43 mmole) sample of anhydro base IIIc was dissolved by boiling in 90 ml of isopropyl alcohol, and the resulting solution was refluxed for 2 h, after which it was allowed to stand at 4° for 24 h. Workup gave 11 g (85.7%) of a product with mp 169-171° (from acetone). Found: C 73.1; H 5.9%. $C_{18}H_{17}NO_3$. Calculated: C 73.2; H 5.8%.

2-(p-Bromophenyl)-7-ethoxycarbonylindolizine (IVe). This compound, with mp 156-157° [from ethanol–dimethylformamide (DMF)], was similarly obtained in 97.5% yield. Found: C 59.3; H 4.0%. $C_{17}H_{14}BrNO_4$. Calculated: C 59.3; H 4.1%.

2-(p-Nitrophenyl)-7-ethoxycarbonylindolizine (IVd). A suspension of 5.9 g (18 mmole) of anhydro base IIId in 10 ml of DMF was refluxed for 30 min, during which the color of the solid material changed from bright-red to yellow. The mixture was then cooled, and the crystals were removed by filtration to give 4 g (72%) of a product with mp 176-177° (from ethanol–DMF). Found: C 65.7; H 4.6; N 9.2%. $C_{17}H_{14}N_2O_4$. Calculated: C 65.8; H 4.6; N 9.0%.

2-(p-Methoxyphenyl)indolizine-7-carboxylic Acid Hydrazide. A suspension of 1 g (3.4 mmole) of IVc in 10 ml of hydrazine hydrate was refluxed for 15 h, after which the solid material was removed by filtration and washed thoroughly with water to give 0.9 g (95%) of a product with mp 253-255°. Found: C 68.2; H 5.4; N 15.0%. $C_{16}H_{15}N_3O_2$. Calculated: C 68.3; H 5.4; N 14.9%.

2-Phenyl-3-formyl-7-ethoxycarbonylindolizine (V). A 0.58-g (3.8 mmole) sample of phosphorus oxychloride was added to 1.1 g of DMF, and the resulting solution was allowed to stand at 18-20° for 15 min, after which the temperature was lowered to 2-5°, and a solution of 1 g (3.8 mmole) of IVb in 20 ml of DMF was added. The mixture was then stirred at 20° for 4h, after which it was poured over ice. The resulting mixture was neutralized with 2 N sodium hydroxide solution, and the precipitate was separated to give 0.95 g (86%) of a product with mp 138-140° (from isopropyl alcohol). Found: C 73.8; H 5.2; N 4.7%. $C_{18}H_{15}NO_3$. Calculated: C 73.7; H 5.2; N 4.8%.

2-Methyl-3-formyl-7-ethoxycarbonylindolizine (VI). This compound, with mp 71-73° (from heptane), was similarly obtained in 42% yield. Found: C 66.9; H 5.5%. $C_{13}H_{13}NO_3$. Calculated: C 67.1; H 5.7%.

2-(p-Methoxyphenyl)-3-acetyl-7-ethoxycarbonylindolizine (VII). A solution of 1.7 g (5.8 mmole) of IVc in 30 ml of acetic anhydride was refluxed for 20 h, after which the mixture was vacuum evaporated, and the residue was mixed with 25% potassium carbonate solution. The potassium carbonate solution was then extracted with ether to give 1.7 g (88%) of a product with mp 133-135° (from heptane). Found: C 71.2; H 5.6%. $C_{20}H_{19}NO_4$. Calculated: C 71.2; H 5.7%.

2-(p-Methoxyphenyl)-3-benzoyl-7-ethoxycarbonylindolizine (VIII). A 1.5-g (5 mmole) sample of IVc was heated with 10 ml of benzoyl chloride at 80-90° for 2 h, after which the mixture was dispersed in 150 ml of petroleum ether. The resulting precipitate was removed by filtration and washed with petroleum ether to give 1.5 g (74%) of a product with mp 104-105° (from ethanol). Found: C 75.1; H 5.3%. $C_{25}H_{21}NO_4$. Calculated: C 75.2; H 5.3%.

Compounds IX-XII were similarly obtained.

2-(p-Bromophenyl)-3-benzoyl-7-ethoxycarbonylindolizine (IX). This compound, with mp 128-130° (from ethanol), was similarly obtained in 82% yield after reaction for 4 h. Found: C 63.9; H 3.9; Br 17.4%. $C_{24}H_{18}BrNO_3$. Calculated: C 64.2; H 4.0; Br 17.8%.

2-(p-Methoxyphenyl)-3-(p-chlorobenzoyl)-7-ethoxycarbonylindolizine (X). This compound, with mp 150-151° (from ethanol), was similarly obtained in 78.5% yield after reaction for 5 h. Found: C 69.0; H 4.7; Cl 8.1%. $C_{25}H_{20}ClNO_4$. Calculated: C 69.2; H 4.7; Cl 8.2%.

2-(p-Bromophenyl-3-(p-chlorobenzoyl)-7-ethoxycarbonylindolizine (XI). This compound, with mp 158-159° (from ethanol), was similarly obtained in 95% yield after reaction for 8 h. Found: C 59.5; H 3.5%. $C_{24}H_{17}BrClNO_3$. Calculated: C 59.7; H 3.6%.

2-(p-Nitrophenyl)-3-(p-chlorobenzoyl)-7-ethoxycarbonylindolizine (XII). This compound, with mp 168-169° (from ethanol), was similarly obtained in 82.5% yield after reaction for 8 h. Found: C 64.3; H 3.9; Cl 7.9; N 6.2%. $C_{24}H_{17}ClN_2O_5$. Calculated: C 64.2; H 3.8; Cl 7.9; N 6.3%.

2-Phenyl-3-dimethylaminomethyl-7-ethoxycarbonylindolizine (XIII). A solution of 2 g (7.5 mmole) of IVb and 2.14 g (21 mmole) of bis(dimethylamino)methane in 50 ml of dioxane was refluxed for 40 h, after which it was vacuum evaporated, and the residue was dissolved in ether–petroleum ether (1:1). The solution was then allowed to stand at 4° for 3 days, after which it was worked up to give 1.7 g (70%) of a product with mp 59-60° (from petroleum ether). Found: C 74.5; H 6.9; N 8.6%. $C_{20}H_{22}N_2O_2$. Calculated: C 74.5; H 6.9; N 8.7%.

2-Phenyl-3-nitroso-6-ethoxycarbonylindolizine (XIV). A 1.4-ml sample of a 20% alcohol solution of hydrogen chloride was added to a solution of 1 g (3.8 mmole) of IVb in 50 ml of DMF, after which the temperature was lowered to 0 to 5°, and 0.66 g (5.6 mmole) of isoamyl nitrite was added. The mixture was then stirred at 20° for 1 h, after which it was cooled and diluted with a double volume of water. The resulting precipitate was removed by filtration and washed with water to give 0.95 g (86%) of a product with mp 153-155° (from isopropyl alcohol). Found: C 69.4; H 4.8; N 9.4%. $C_{17}H_{14}N_2O_3$. Calculated: C 69.4; H 4.8; N 9.3%.

LITERATURE CITED

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SYNTHESIS AND PROPERTIES OF NICOTINIC ACID DERIVATIVES CONTAINING A 2,2,6,6-TETRAMETHYLPIPERIDINE 1-OXYL RESIDUE

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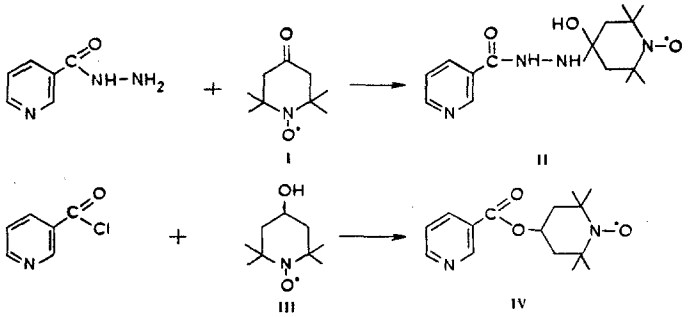
N^1-(Nicotinoyl)-N^2-4-(2,2,6,6-tetramethyl-4-hydroxypiperidine-1-oxyl)hydraxine was obtained by condensation of nicotinoyl hydrazide with 2,2,6,6-tetramethyl-4-oxopiperidine 1-oxyl. Acylation of 2,2,6,6-tetramethyl-4-hydroxypiperidine 1-oxyl with nicotinoyl chloride gives nicotinic acid 2,2,6,6-tetramethyl-1-oxyl 4-piperidyl ester. A spin-labeled analog of nicotinamide was obtained by condensation of nicotinoyl azide with 4-amino-2,2,6,6-tetramethylpiperidine 1-oxyl. The synthesis of 1-N-(β-D-ribofuranoside)-3'-N[4-(2,2,6,6-tetramethylpiperidine-1-oxyl)]pyridinecarboxamide from 2,2,6,6-tetramethyl-4-nicotinoylaminopiperidine 1-oxyl and 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide proceeds without damage to the iminoxyl radical. The preparation of the corresponding spin-labeled nucleotide is hindered by destruction of the iminoxyl radical during ion-exchange chromatography.

A number of authors has shown the possibility of the synthesis of various compounds containing a stable iminoxyl radical [1]. The synthesis of spin-labeled derivatives of a biologically active substance such as nicotinic acid seems of undoubted interest. Compounds II and IV were synthesized by traditional methods in 33 and 64.5% yields, respectively.



I II III IV

The starting compound for the synthesis of IV is 2,2,6,6-tetramethyl-4-aminopiperidine 1-oxyl (V), which is obtained by the method in [2]. Replacement of the steam-distillation step in the isolation of 2,2,6,6-tetramethyl-4-aminopiperidine by extraction with ether from a saturated alkaline solution made it possible to considerably shorten the synthesis time and raise the yield of the product from 29% to 70%.

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