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ELECTROCHEMICAL REDUCTION OF 5-OXOINDENO[1,2-*b*]PYRIDINIUM PERCHLORATES IN THE PRESENCE OF ALKYLATING AGENTS

B. Turovska, D. Muceniece, V. Lusis, I. Turovskis, E. Liepin'sh, and J. Stradins

It was established that 9b-substituted 5,9b-dihydroindenopyridines are formed in addition to the reduction products on preparative electrochemical reduction of 5-oxoindeno[1,2-b]pyridinium perchlorates at a mercury electrode in acetonitrile in the presence of alkylating agents.

Keywords: 5,9b-dihydro-5-oxoindeno[1,2-*b*]pyridine, indenopyridinium perchlorates, electrochemical reduction.

At the end of the seventies H. Lund showed [1] that certain readily oxidizable anions, generated in the process of electrochemical reduction, are electron donors capable of reacting with alkyl halides by the following scheme.

$$A^+ + e \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^\bullet$$

$$A^\bullet + e \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} A^-$$

$$A^- + BX \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A^\bullet + BX^{\bullet -}$$

$$BX^{\bullet -} \xrightarrow{k_4} B^\bullet + X^-$$

$$A + B^{\bullet\bullet} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} AB$$

The scheme was used [1,2] in the example of 1-ethyl-4-methoxycarbonylpyridinium iodide, which is reduced in two sequential reversible one-electron stages. 4-Alkyl-1-ethyl-4-methoxycarbonyl-1,4-dihydropyridines are the reduction products prepared in the presence of various alkyl halides.

In the present work values have been determined for the half-wave potentials in the electrochemical reduction of certain 5-oxoindeno[1,2-*b*]pyridinium perchlorates **1a-f** and the reduction of the most available salt **1c** has been studied in the presence of alkylating agents.

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: turovska@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1819-1826, December, 2003. Original article submitted September 22, 2003.

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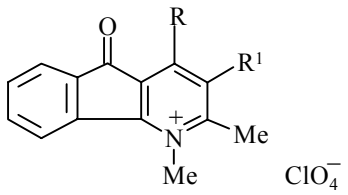
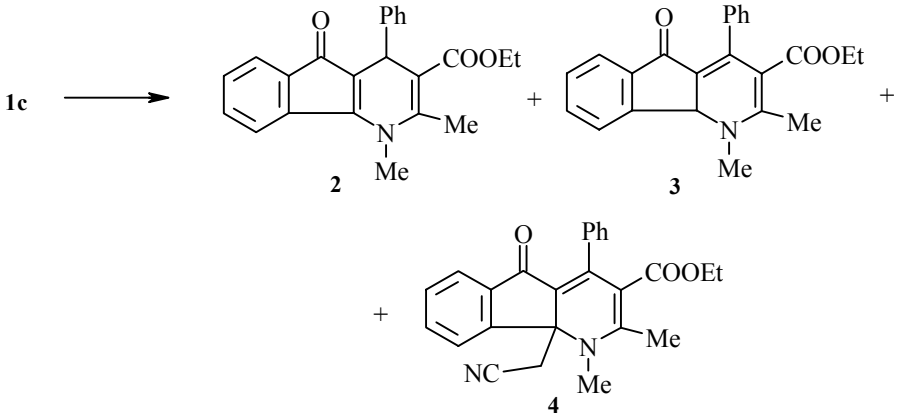


1a–f

1a, **c**, **f** R = Ph, **b** R = H, **d** R = C_6H_4OMe-*p*, **e** *R* = C_6H_4OMe-*p*; **a** R^1 = H, **b–e** R^1 = COOEt, **f** R^1 = CN

In acetonitrile the reduction of the investigated compounds proceeds in two sequential one-electron quasireversible stages (Table 1). The nature of the reduction waves and the products formed at potentials beyond the second polarographic wave were not investigated in this work.

Dihydropyridines **2** and **3** and the 9b-cyanomethyl derivative **4** of indenopyridine were isolated and identified as products of the preparative electrolysis at the potential of the second stage of the reduction of compound **1c** in acetonitrile. The yield of each of the products was ~20%.



The appearance of compound **4** on reducing salt **1c** may be represented as being due to the interaction of free radicals generated from the indenopyridine and MeCN. The formation of an indenopyridine radical is due to the process of one-electron electroreduction, and the generation of a $\cdot CH_2CN$ radical from acetonitrile in electrochemical reactions is also unknown [3].

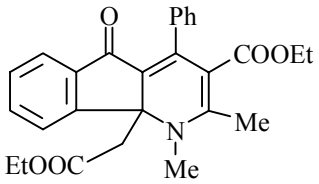
TABLE 1. Values of the Peak Potentials (E_p) for the Electrochemical Reduction of Salts **1a-f** at the Stationary Pt Electrode in Acetonitrile*

Compound	E_p, V		Compound	E_p, V	
	1st stage	2st stage		1st stage	2st stage
1a	-0.64	-1.35	**1d**	-0.60	-1.32
1b	-0.60	-1.32	**1e**	-0.52	-1.25
1c	-0.61	-1.33	**1f**	-0.40	-1.18

* Base electrolyte was 0.1 M $TBABF_4$, depolarizer concentration $c = 5 \cdot 10^{-4}$ M.

In the presence of alkylating agents the electrochemical characteristics of the investigated compounds are changed. The established potential for the electrochemical reduction of chloroacetic acid ethyl ester (-1.5 V) indicates that the irreversible process for the direct reduction of this compound is more difficult than both stages of all the investigated compounds **1a-f** (Table 1). None the less the addition of $ClCH_2COOEt$ (about 20 μl) to a solution of **1a** (10 ml: $2.5 \cdot 10^{-4}$ M) led to an increase in the height of the second reduction wave of indenopyridinium perchlorate **1a** (Fig. 1). The potentials of both reduction stages of compound **1a** were practically unchanged, but the second stage became less reversible.

A similar effect is also observed in the case of the electrochemical reduction of the pyridinium salt **1c** studied by cyclic voltammetry in the presence of chloroacetic acid ethyl ester (Fig. 2). After electrolysis of compound **1c** at a controlled potential (-1.4 V) in the presence of $ClCH_2COOEt$ at a consumption of 4.16 F/mol, indenopyridines **5** (21% yield) and **6** (<5%) were isolated and identified, in addition to reduction products **2-4** formed also in the absence of $ClCH_2COOEt$.



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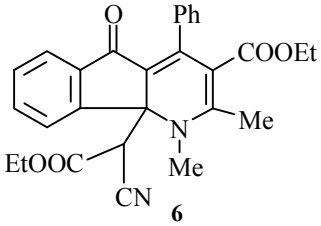

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The catalytic increase of the second wave for the investigated compounds in the presence of $ClCH_2COOEt$ indicates that the indenodihydropyridinium anion (the product of the second reduction stage) is capable of reducing chloroacetic acid ethyl ester in spite of the fact that the potential of the direct cathodic reduction of the latter is displaced towards a more negative potential by ~0.4 V. The dihydropyridine anion is

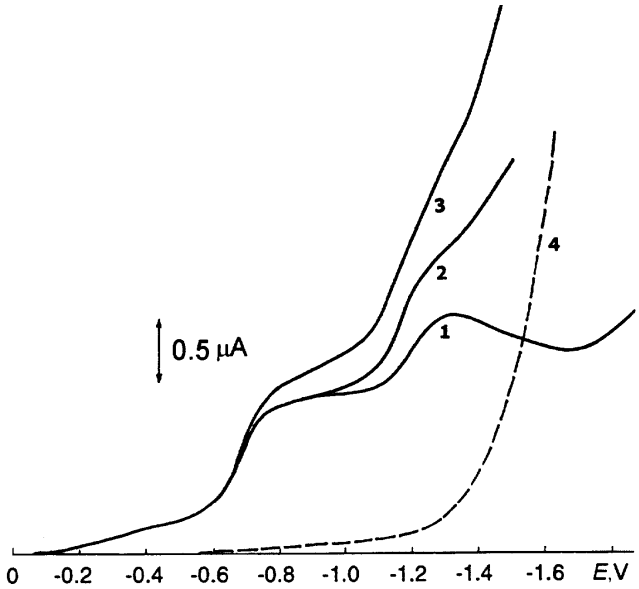


Fig. 1. 1) Electrochemical reduction of salt **1a** ($c = 2.5 \cdot 10^{-4}$ M) at the dropping mercury electrode (DME) in $MeCN–TBABF_4$ and 2) in the presence of 20 μl and 3) 40 μl $ClCH_2COOEt$.
4) Electrochemical reduction of $ClCH_2COOEt$ ($c = 5 \cdot 10^{-4}$ M) in $MeCN–TBABF_4$.

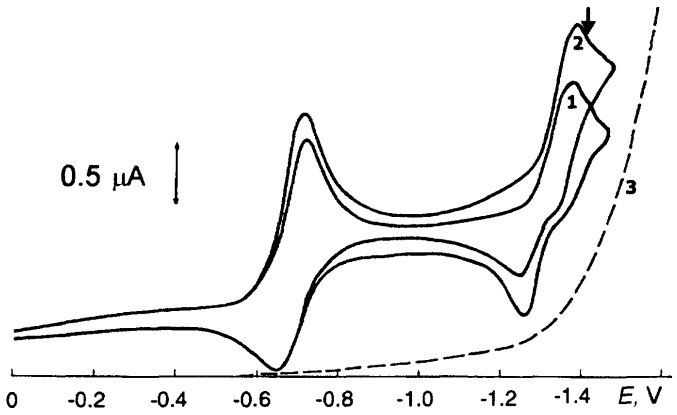


Fig. 2. Cyclic voltammetric curves at the stationary Pt electrode for salt **1c** ($c = 5 \cdot 10^{-4}$ M) in 1) MeCN–$TBABF_4$, and 2) in the presence of $ClCH_2COOEt$ (20 μl). 3) Electrochemical reduction of $ClCH_2COOEt$ ($c = 1 \cdot 10^{-2}$ M) in MeCN–$TBABF_4$. The potential of preparative electrolysis is shown by the arrow.

thereby reversibly oxidized to the free radical which causes growth in the height of the second wave. Fission of the C–Cl bond occurs in the molecule of alkylating agent being reduced and a reactive radical is formed. According to the data of [1, 4, 5] the mechanism of interaction of an electrochemically generated nucleophile with an electrophile is determined by the difference in the potentials for oxidation of the anion and reduction of the chosen alkyl halide. If the difference of the potentials is less than 0.5 V then nucleophilic substitution occurs by a one-electron SET transfer machanism.

$$A^- + BX \longrightarrow [A^\bullet + B^\bullet + X^-] \longrightarrow AB + X^-$$

At a difference of potentials greater than 0.5 V the mechanism is close to the S_N2 type.

$$A^- + BX \longrightarrow [A \bullet\bullet\bullet B \bullet\bullet\bullet X]^- \longrightarrow AB + X^-$$

Both mechanisms may operate simultaneously over a certain range of differences of potential.

Since the difference of potentials of the investigated **1c**–$ClCH_2COOEt$ pair is less than 0.5 V and in the course of the reaction regeneration of pyridyl radicals is observed, it may be suggested that substitution product **5** is formed by the SET variant of nucleophilic substitution. In favor of this proposal is the fact that electrolysis at the potential of the first reduction stage of the indenopyridinium salt in the presence of ethyl chloroacetate does not lead to the formation of derivative **5**. Consequently compound **5** is not formed without the participation of indenopyridyl anion.

A case when the substitution mechanism is shifted into the S_N2 region is the electrolysis of the indenopyridinium salt **1c** in the presence of chloroacetonitrile. The difference of potentials of the **1c**–$ClCH_2CN$ pair at 0.5 V is in the adjacent mechanism region. The height of the second reduction wave on adding chloroacetonitrile was increased insignificantly, which indicates the absence of regeneration of nascent pyridyl radicals. In addition, a reduction in the reversibility of this reduction step is evident from the cyclic voltamperogram (Fig. 3). In this case a third irreversible reduction wave is also displayed, indicating the appearance of a new product. However on preparative electrolysis carried out at the potential of this third wave (-1.58 V), only the known indenopyridines **2-4** were isolated. It was impossible to clarify the mechanism of formation of compound **4** on the basis of the few electrochemical data [1].

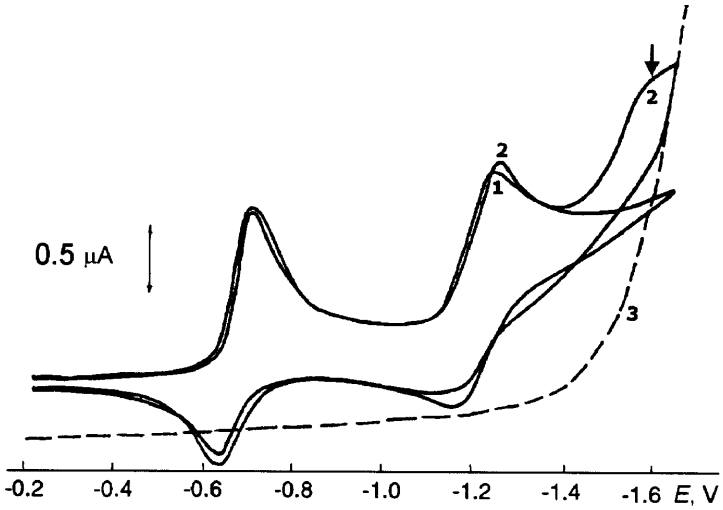


Fig. 3. Cyclic voltammetric curves at the stationary Pt electrode for salt **1c** ($c = 5 \cdot 10^{-4}$ M) in 1) MeCN–$TBABF_4$ and 2) in the presence of $ClCH_2CN$ (20 μl). 3) Electrochemical reduction of $ClCH_2CN$ ($c = 1 \cdot 10^{-2}$ M) in MeCN–$TBABF_4$. The potential for preparative electrolysis is shown by the arrow.

It should also be noted that derivative **4**, as already mentioned above, is also formed as a result of a radical process proceeding in parallel. In favor of the formation of indenopyridine **4** by replacement of chlorine in the $ClCH_2CN$ molecule by an electrochemically generated nucleophile, is the increase in yield of the product (35%) compared with the yield obtained on electrolysis in the absence of chloroacetonitrile.

Products of addition of methane halogen derivatives to the 9b-C of the indenopyridine ring are also isolated on carrying out preparative electrochemical reduction in the presence of chloroform and carbon tetrachloride. Since $CHCl_3$ and CCl_4 are reduced at lower potentials (-0.80 and -0.65 V respectively) than the indenopyridyl radical, it is not possible to develop a catalytic increase of the second reduction wave (Fig. 4).

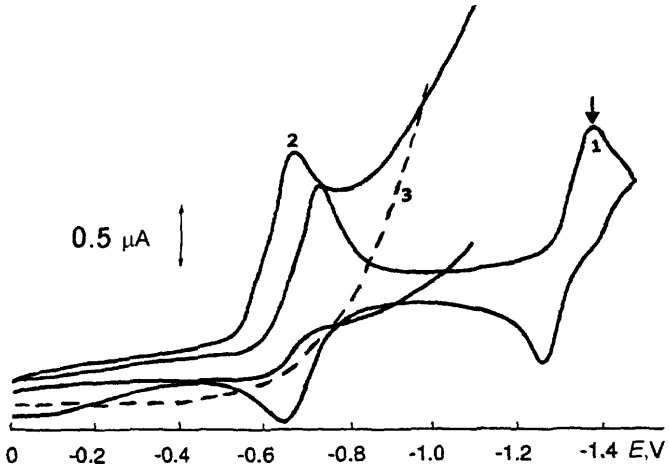
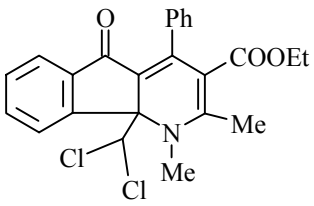


Fig. 4. Cyclic voltammetric curve at the stationary Pt electrode 1) for salt **1c** ($c = 5 \cdot 10^{-4}$ M) in MeCN–$TBABF_4$ and 2) in the presence of $CHCl_3$ (20 μl). 3) Electrochemical reduction of $CHCl_3$ ($c = 2 \cdot 10^{-2}$ M) in MeCN–$TBABF_4$. The potential for the preparative electrolysis is indicated by the arrow.

The formation of 9b-substituted indenopyridines **7** (23% yield) and **8** is possible both as a result of the recombination of radicals, generated electrochemically, and on participation of pyridyl anion, similar to the reaction with chloroacetic acid ester.

On carrying out the reduction in the presence of CCl_4, as well as addition of $\cdot CCl_3$ to the 9b-C atom of the indenopyridine, substitution of a hydrogen atom by the CCl_3 fragment occurs at the 2-methyl group and compound **8**, which is poorly stable, is formed, indicating the presence of a significant quantity of trichloromethyl radicals in the reaction medium.

The chemical shifts of the N–CH_3 and 2-CH_3 groups and of the aromatic protons in the ^{1}H NMR spectra of compounds **4-8** differ little from those of the indenodihydropyridine **3** [6], which makes it possible to establish the structure of the obtained 9b-substituted indenodihydropyridines. In the spectra of compounds **4** and **5** the protons of the methylene groups are displayed as two doublets (AB system), unlike compound **3** in the spectrum of which there is a singlet corresponding to the proton at 9b-C. The structure of indenopyridine **8** was confirmed by the absence of singlets corresponding to the signal of the protons at 9b-C and 2-C and by the appearance of doublets at 4.11 and 5.44 ppm. The ^{1}H NMR spectra of compounds **4** and **6** also indicate the presence of two ester groups in the molecules. In addition the HMBC spectrum of product **6** indicates that the methane carbon is associated with the 9b-C atom (69.5 ppm), with the ester group carbon (168.4 ppm), and also with the nitrile carbon (C≡N) (113.1 ppm) and thereby confirms the presence of two functional groups in the substituent at the 9b-C atom in the dihydropyridine **6** molecule.



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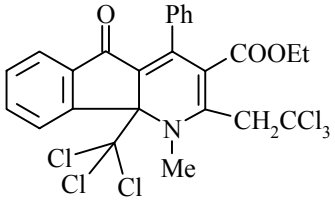

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Consequently 9b-substituted 5,9b-dihydroindeno[1,2-*b*]pyridines are formed as a result of electrochemical reduction of oxoindenopyridinium salts in the presence of alkylating agents. These are compounds which are not successfully obtained by classical organic synthesis up to the present time.

EXPERIMENTAL

The electroreduction processes were studied with the aid of a PAR 170 electrochemical system by a three-electrode scheme using classical polarography at the dropping mercury electrode (DME), cyclic voltammetry at the stationary Pt electrode, and also preparative electrolysis at a stirred mercury base at constant potential. The dissolved oxygen was removed from solutions by purging with argon.

Polarograms were taken on the DME, a Pt wire was used as anode. In cyclic voltammetry a Pt disk (d = 2 mm) was used as anode. In preparative electrolysis in an H-shaped cell a stirred mercury base served as cathode, the anode was a graphite rod. In all cases potentials were measured relative to a saturated aqueous calomel electrode fitted with a salt bridge. Freshly distilled (from CaH_2) acetonitrile was used, tetrabutylammonium tetrafluoroborate ($TBABF_4$) served as base electrolyte. Chromatography was carried out on silica gel 0.035-0.070 mm (Acros).

The NMR spectra were taken on a Bruker WH 90 (90 MHz) spectrometer, but the spectrum of product **6** was taken on a Bruker WH 600 (600 MHz) in $CHCl_3$, internal standard was TMS. Mass spectra were obtained on a MS 50 instrument.

Indenopyridinium Perchlorates 1c-f were obtained by the procedure of [7].

General Procedure for the Preparative Electrolysis of Indenopyridinium Salt 1c. Electrolysis was carried out in 0.1 M $TBABF_4$ solution in acetonitrile (100 ml) at the potential of the second reduction wave of compound **1c** (-1.3 V) in a current of argon. The H-shaped cell was filled with base electrolyte solution. The pyridinium salt (1.0 g, 2.2 mmol) was introduced into the cathode compartment. After the end of the electrolysis the reaction mixture was evaporated, and to separate the electrolyte the residue, dissolved in chloroform (10 ml), was put onto a column (4 × 50 cm) of silica gel and eluted with chloroform. The chloroform (0.7-1.0 l) was evaporated, and the residue subjected to column chromatography (column 2 × 70 cm, eluent was chloroform–hexane–acetone, 9:7:1). Red indenopyridine **2** was isolated from the first fraction and yellow indenopyridine **3** from the second fraction. The fraction containing the addition product **4** was then collected.

In the case of reduction in the presence of alkylating agent, an excess (10 ml) of it was added to the pyridinium salt **1c** solution in the cathode compartment. The reaction mixture was processed and the products isolated analogously to the previous experiment. On chromatography the alkylation products were isolated from the fractions following the fraction of indenopyridine **3**. The ^{1}H NMR spectra of the isolated indenopyridines **2** and **3** were identical to those described previously in [6,8].

Ethyl Ester of 9b-Cyanomethyl-1,2-dimethyl-5-oxo-4-phenyl-5,9b-dihydro-1H-indeno[1,2-*b*]-pyridine-3-carboxylic Acid (4). Mp 197-199°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.62 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 2.22 (1H, d, *J* = 17.0, CH_2); 2.68 (3H, s, CH_3); 3.33 (3H, s, NCH_3); 3.37 (1H, d, 17.0, CH_2); 3.73 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 7.20-7.80 (9H, m, H_{arom}). IR spectrum, ν, cm^{-1}: 2240 (C≡N); 1690, 1670 (C=O). Found, %: C 74.98; H 5.44; N 6.79; *m/z* 398 $[M]^+$. $C_{25}H_{22}N_2O_3$. Calculated, %: C 75.36; H 5.57; N 7.03; M = 398.

Ethyl Ester of 9b-Ethoxycarbonylmethyl-1,2-dimethyl-5-oxo-4-phenyl-5,9b-dihydro-1H-indeno-[1,2-*b*]pyridine-3-carboxylic Acid (5). Mp 140-141°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.57 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 1.11 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 2.51 (1H, d, *J* = 15.0, CH_2); 2.64 (3H, s, CH_3); 3.17 (1H, d, *J* = 15.0, CH_2); 3.22 (3H, s, NCH_3); 3.70 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 4.00 (2H, q, $OC\underline{H}_2CH_3$); 7.30-7.90 (9H, m, H_{arom}). IR spectrum, ν, cm^{-1}: 1740, 1690, 1670 (C=O). Found, %: C 72.55; H 6.21; N 3.11; *m/z* 445 $[M]^+$. $C_{27}H_{27}NO_5$. Calculated, %: C 72.79; H 6.11; N 3.14; M = 445.

Ethyl Ester of 9b-Cyanoethoxycarbonylmethyl-1,2-dimethyl-5-oxo-4-phenyl-5,9b-dihydro-1H-indeno[1,2-*b*]pyridine-3-carboxylic Acid (6). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.62 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 1.43 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 2.67 (3H, s, CH_3); 3.24 (3H, s, NCH_3); 3.73 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 4.37 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 5.00 (1H, s, CH); 7.40-7.86 (9H, m, H_{arom}). IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1745, 1695, 1680 (C=O).

Ethyl Ester of 9b-Dichloromethyl-1,2-dimethyl-5-oxo-4-phenyl-5,9b-dihydro-1H-indeno[1,2-*b*]-pyridine-3-carboxylic Acid (7). Mp 187-189°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.65 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 2.64 (3H, s, CH_3); 3.37 (3H, s, NCH_3); 3.76 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 6.24 (1H, s, CH); 7.20-8.20 (9H, m, H_{arom}). Found: *m/z* 405 $[M\text{-}HCl]^+$. $C_{24}H_{21}Cl_2NO_3$. Calculated: M = 441.

Ethyl Ester of 1-Methyl-2-(2,2,2-trichloroethyl)-9b-trichloromethyl-5-oxo-4-phenyl-5,9*b*-dihydro-1H-indeno[1,2-*b*]pyridine-3-carboxylic Acid (8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.55 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 3.55 (3H, s, NCH_3); 3.55 (2H, q, *J* = 7.5, $OC\underline{H}_2CH_3$); 4.11 (1H, d, *J* = 16.0, CH_2); 5.44 (1H, d, *J* = 17.0, CH_2); 7.10-8.20 (9H, m, H_{arom}). Found: *m/z* 520 $[M\text{-}HCl\text{-}Cl]^+$. $C_{25}H_{19}Cl_6NO_3$. Calculated: M = 591.

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