SYNTHESIS OF 3H-PYRROLO[2,3-c]ACRIDINE AND SOME OF ITS PROPERTIES*

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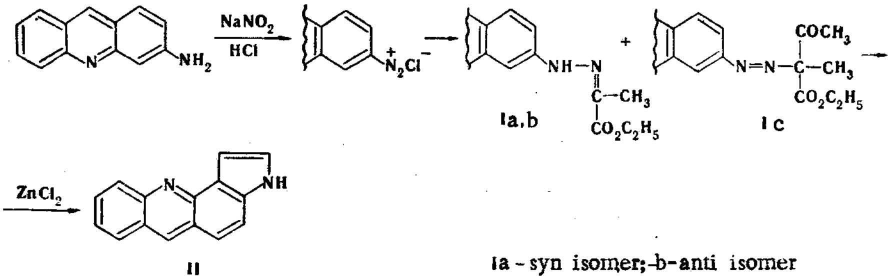
The present work describes the synthesis of the new heterocyclic system of 3H-pyrrolo[2,3-c]acridine (II), the investigation of its physicochemical characteristics, and its behavior in some electrophilic substitution reactions.

Compound (II) was obtained by the scheme given below by means of the Japp–Klingemann and Fischer reactions. It is known that the reaction of diazonium salts with compounds containing an activated methine group is a two-stage process involving the formation of an azo compound, which readily changes into the corresponding hydrazone under the reaction conditions [2, 3]. A series of authors have been able to isolate the intermediately formed azo derivatives [4, 5].



Ia - syn isomer; b-anti isomer

The dark-red viscous oil which we obtained by coupling acridinediazonium with methylacetoacetic ester is also a mixture of an azo compound with hydrazones. The syn and anti isomers of ethyl pyruvate 3-acridinylhydrazone (Ia, b) and ethyl α-(acridinylazo)-α-acetylpropionate "azo ester" (Ic) were isolated by chromatography.

In contrast to 3-acridinylhydrazones, in the IR spectrum of compound (Ic) there are two strong absorption bands for the carbonyl group in the regions of 1690 and 1710 cm^{-1}, which can be assigned to the frequencies of the acetyl and ethoxycarbonyl groups respectively [6], and a weak absorption band for the —N=N— bond appears in the region of 1510 cm^{-1}, whereas the absorption band of the NH bond disappears. In the UV spectrum of the "azo ester" (Ic) we identified the characteristic absorption maximum of the phenylazo group in the region of 283 nm [5], which undergoes a hypsochromic shift compared with the syn and anti forms of the hydrazone. When compound (Ic) was boiled in ethanol which had been acidified with hydrochloric acid, the transition from the "azo ester" to the anti form of the 3-acridinylhydrazone, identical with that isolated from the mixture of isomers, was observed, and this also confirms the structure of compound (Ic). The presence of an intramolecular hydrogen bond in the case of the syn isomer of the 3-acridinylhydrazone introduces differences into the IR, UV, and PMR spectra of the isomeric hydrazones. In the IR spectrum of compound (Ia), recorded in chloroform, the absorption bands of the C=O and NH groups are shifted toward lower frequencies compared with the IR spectrum of compound (Ib). In addition, the split absorption band of the NH group was observed in the IR spectrum of the syn isomer, and it had higher intensity than that of the anti isomer. In the UV spectrum of the syn isomer there was a bathochromic shift of the long-wave absorption band, typical of stereoisomeric hydrazones [7]. In the PMR spectra of the hydrazones there was a small downfield shift of the signals for the protons of the methyl and NH groups in the case of the syn isomer, and this also confirms

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*For the preliminary communication, see [1].

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TABLE 1. Chemical Shifts (δ, ppm) and Spin–Spin Coupling Constants (J, Hz) of 3H-Pyrrolo[2,3-c]acridine and its Derivatives

Compound	Solvent	δ, ppm											J, Hz
		1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	$\Delta\delta_{4,5}$	
II	DMSO-d_6	7,29	7,41	11,79	7,68	7,68	8,97	8,08	7,72	7,72	8,16	—	$J_{1,2}=3,0$; $J_{2,3}=2,6$; $J_{1,3}=2,3$
II	CCl_4—DMSO-d_6 (9 : 1)	7,19	7,31	11,28	7,50	7,59	8,63	7,9	7,42	7,42	8,13	9,1	$J_{1,2}=3,0$; $J_{2,3}=2,6$; $J_{1,3}=2,3$; $J_{4,5}=8,9$
III	DMSO-d_6	—CH_2— 4,26 —$N(CH_3)_2$ 2,27	7,23	11,62	7,62	7,62	8,86	8,01	7,57	7,57	8,10	—	
IV	DMSO-d_6	CHO 11,44	8,10	—	7,81	7,73	9,05	8,06	7,63	7,63	8,18	8,4	$J_{4,5}=8,8$
V	DMSO-d_6	7,46	7,94	$COCH_3$ 2,80	8,51	7,91	9,01	8,10	7,68	7,68	8,18	60,3 —	$J_{1,2}=3,4$; $J_{4,5}=9,0$
VI	d-methanol	H_{11} — 8,28 H_{12} — 7,71	7,50	—	7,75	7,75	9,27	7,8—8,2					$J_{11,12}=8,0$

that the NH proton participates in the formation of an intramolecular hydrogen bond.

We were able to realize the indolization of 3-acridinylhydrazone and of the "azo ester" in molten zinc chloride. As a result we obtained unsubstituted 3H-pyrrolo[2,3-c]acridine with a yield of 15-20%. The low yield of compound (II) was evidently due to thermal degradation of the acridinylhydrazone and also to the acidophobic character of the pyrroloacridine itself. In addition to compound (II), we isolated 3-aminoacridine from the reaction mixture, and this is consistent with the mechanism of decomposition of hydrazones under these conditions [8].

The signals in the PMR spectrum of compound (II) were assigned and the direction of coupling in the pyrrole and acridine rings was established by comparison with the PMR data for indole and its condensed derivatives (benzo- and pyridoindoles [9, 10]). The signal for the proton at the nitrogen atom of the pyrrole ring in the PMR spectrum recorded in DMSO-d_6 (Table 1) lies in the downfield region of the spectrum (δ 11.79 ppm), and this agrees well with published data [9, 10]. Signals at 7.29 and 7.41 ppm can be assigned to the 1-H and 2-H protons respectively. This follows from examination of their multiplicity ($J_{2,3} > J_{1,3}$) and from comparison with the chemical shifts of the analogous protons in pyrroloquinolines [9, 11]. A singlet with double intensity in the region of 7.68 ppm belongs to the protons of the benzene ring condensed with the pyrrole ring, since the quartet of an AB system of these protons with J_{AB} = 8.9 Hz, Δδ = 9.1 Hz, characteristic of 4,5-condensed derivatives of indole [10, 11], is observed when the solvent is replaced by a 9:1 mixture of carbon tetrachloride and DMSO-d_6. This makes it possible to conclude that the pyrrole ring forms an angular arrangement in relation to the acridine ring. The assignment of the signal at δ 8.97 ppm to the 6-H proton is obvious from comparison with the spectrum of acridine [12]. The assignment of the signals for the 7-H, 8-H, 9-H, and 10-H protons, which represent an ABRX system, was made by comparison with the spectra of benzindoles [9].

The strongest shortwave maximum in the UV spectrum of compound (II) (278 nm) undergoes a bathochromic shift of 12 nm, compared with the UV spectrum of acridine [12]. Replacement of the nonpolar solvent by a polar solvent does not have a significant effect on the position of the bands, and this is evidently due to the low ability of pyrroloacridine to form associates with the solvent.

The basicity constant of compound (II) (pK_a 6.86) is considerably higher than the constant of acridine and isomeric pyrroloquinolines [13, 14]. The fluorescence spectrum of pyrroloacridine has less structure and is shifted toward the long-wave region compared with the spectra of indole and acridine (Fig. 1). The magnitude of the shift is of the same order as for the spectra of pyrroloquinolines. The phosphorescence spectrum is similarly shifted toward the long-wave region (468-478 nm) compared with the spectrum of indole, and this corresponds to the position of the main maxima in the spectra of pyrroloquinolines [14].

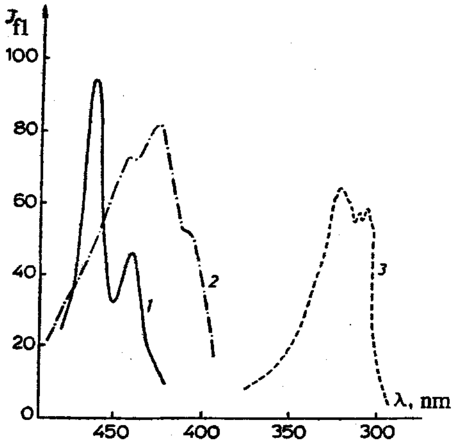


Fig. 1. Fluorescence spectra: 1) 3H-Pyrrolo[2,3-c]acridine; 2) acridine; 3) indole.

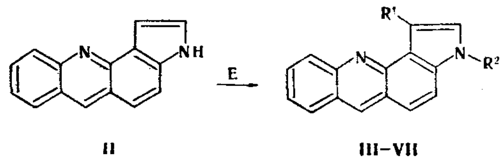
TABLE 2. Absorption Band of the NH group of Indole and 3H-Pyrrolo[2,3-c]acridine (II) in the Presence of Some Proton Acceptors

Compound	ν, cm^{-1}				
	Vaseline oil	$CHCl_3$	THF	$CH_3C{\equiv}N$	CH_3COCH_3
Indole	3390	3495 (free NH) 3410 (combined NH)	3300	3350	3410
II	3180	3480 (free NH) 3320 (combined NH)	3310	3400	3420

In the IR spectrum of 3H-pyrrolo[2,3-c]acridine, recorded in chloroform, the band for the free NH group appears in the region of 3480 cm^{-1}, and the band for the combined NH group appears at 3180 cm^{-1} for a paste in Vaseline oil and at 3320 cm^{-1} in chloroform. In the presence of strong proton acceptor, the pyrroloacridine forms associates in which the position of the absorption bands of the NH group is very close to the position of the absorption band of the NH group in the associates of indole (Table 2).

It was interesting to follow the behavior of 3H-pyrrolo[2,3-c]acridine in electrophilic substitution reactions (Mannich, Vilsmeier, acetylation, and azo coupling).

When the Mannich reaction was carried out under the previously described conditions [15], a significant amount of the pyrroloacridine remained in the reaction mixture. By increasing the temperature and reaction time it was possible to increase the yield of 1-dimethylaminomethyl-3H-pyrrolo[2,3-c]acridine (III) to quantitative. In the PMR spectrum of compound (III) the chemical shifts of the 2-H and 3-H protons are shifted upfield compared with (II). A similar behavior for the pyrrole protons was observed in the case of the analogous compounds of pyrroloquinolines with the same fusion of the indole and pyridine rings.



II III-VII

III $R^1=CH_2N(CH_3)_2$; IV $R^1=CHO$; V $R^1=H$; VI $R^1=N_2C_6H_4{-}NO_2\text{-}p$, VII $R^1=N_2C_6H_4{-}Cl\text{-}p$;
III, IV, VI, VII $R^2=H$

By the reaction of the pyrroloacridine with N,N-dimethylformamide under Vilsmeier conditions we obtained 1-formyl-3H-pyrrolo[2,3-c]acridine (IV) with a 60% yield. In the PMR spectrum of compound (IV) there is a characteristic narrow singlet for the aldehyde proton at δ 11.44 ppm in contrast to the broad singlet for the NH proton. Substitution of the 1-H proton by the formyl group greatly shifts the signal for the 2-H proton downfield. The signals of the 4-H and 5-H protons are also affected by the formyl group, and a quartet characteristic of an AB system appears instead of the singlet for these protons in compound (II).

Vilsmeier acylation of compound (II) at the β-carbon atom with N,N-dimethylacetamide was impossible, irrespective of the conditions, and this was clearly due to the lower electrophilicity of this complex and to steric hindrances on the part of the pyridine and benzene rings. It was only possible to realize acylation under the conditions described for indole [16] by increasing the reaction temperature a little. The structure of N-acetyl-3H-pyrrolo[2, 3-c]acridine (V) was confirmed by the IR spectrum, where an absorption band for the acetyl group appeared in the region of 1710 cm^{-1} and there was no band for the stretching vibrations of the NH group. In the PMR spectrum of compound (V) there was strong descreening of the 4-H and 5-H protons, and this was clearly due to the influence of the acetyl substituent.

In the azo coupling reaction benzenediazonium and p-nitro- and p-chlorobenzenediazonium chlorides were used as diazo components. It was found that 3H-pyrrolo[2,3-c]acridine does not enter into reaction with benzenediazonium chloride, whereas it gives small yields of the corresponding azo coupling products (VI, VII) with p-nitro and p-chlorobenzenediazonium chloride.

Thus, it can be concluded that in qualitative respects the reactivity of 3H-pyrrolo[2, 3-c]acridine is significantly lower than that of indole.

EXPERIMENTAL

The UV spectra were recorded on a Specord spectrophotometer. The IR spectra were recorded on a UR-20 spectrophotometer. The PMR spectra were recorded on a Varian HA-100D spectrometer with HMDS as internal standard. The fluorescence spectra were recorded in alcohol solution on a Hitachi EPS-3 instrument with h_{exc} = 450 nm. The phosphorescence spectrum was investigated at 77°C on an SD-1 luminescence spectrophotometer with monochromatic excitation at λ = 472 nm.

3-Acridinylhydrazones of Ethyl Pyruvate and Ethyl α-(Acridinylazo)-α-acetylpropionate (Ia-c). A 9.7-g sample (0.05 mole) of 3-aminoacridine was dissolved in 30 ml of concentrated hydrochloric acid and diazotized with a 20% solution of 4.1 g (0.06 mole) of sodium nitrite, while the temperature was kept between 0 and +5°C by the addition of ice. The mixture was stirred for 30 min, neutralized to pH 5 with sodium acetate, filtered, and rapidly added to a solution of methylacetoacetic ester in 20 ml of isopropyl alcohol and 30 ml of water, to which 3 g (0.055 mole) of potassium hydroxide was added just before coupling. The mixture was stirred at 0-5°C for 1 h and kept at pH 5-6. The oily product was separated by decantation, the aqueous layer was extracted with 300 ml of benzene, and the extract was combined with the main product, dried with sodium sulfate, and chromatographed on a column of aluminum oxide. The eluent for (Ic) was ether. The yield of (Ic) was 1.07 g (7%); mp 238-239°C. UV spectrum (in alcohol), λ_{max} (log ε): 223 (4.38), 239 (4.68), 283 (4.68), 378 nm (4.3). Found, %: C 68.7; H 5.2; N 12.0. $C_{20}H_{19}N_3O_2$. Calculated, %: C 68.7; H 5.4; N 12.0. For (Ia, b) the eluent was a 1:1 mixture of ether and ethyl acetate. The yield of (Ia) was 0.6 g (4%); mp 184-185°C (from ether) IR spectrum (chloroform): 3230, 3270 (NH), 1679 cm^{-1} (CO). UV spectrum (in alcohol), λ_{max} (log ε): 222 (4.22), 243 (4.56), 350 nm (4.54). PMR spectrum (in DMSO): 2.29 (s, $N{=}C{-}CH_3$); 12.26 ppm (s, NH). The yield of (Ib) was 8.4 g (55%) mp 195°C (from ether). IR spectrum (chloroform): 3380 (NH), 1700 cm^{-1} (CO). UV spectrum (in alcohol), λ_{max} (log ε): 223 (4.32), 241 (4.54), 322 (4.54), 383 nm (3.69). PMR spectrum (in DMSO): 2.22 (s, $N{=}C{-}CH_3$); 10.3 ppm (s, NH). Found, %: (Ia), C 70.4; H 5.5; N 13.6; (Ib), C 70.5; H 5.2; N 13.4. $C_{18}H_{17}N_3O_2$. Calculated, %: (Ia, b), C 70.3; H 5.5; N 13.6.

3H-Pyrrolo[2,3-c]acridine (II). A 2-g sample (6.2 mole) of compound (Ia-c) and 2.7 g (0.02 mole) of zinc chloride were fused at 230°C for 5 min and rapidly cooled. A 100-ml portion of water was added, and the precipitate was filtered off and treated to pH 10 with sodium hydroxide solution, washed to a neutral reaction with water, dried, and chromatographed on a colum of silica gel with ether as eluent. The yield was 0.27 g (20%); mp 242°C. Found, %: C 82.9; H 4.6; N 12.7. $C_{15}H_{10}N_2$. Calculated, %: C 82.6; H 4.6; N 12.8. For the IR and UV spectra, see [1].

1-Dimethylaminomethyl-3H-pyrrolo[2,3-c]acridine (III). To 0.6 ml of a 33% aqueous solution of dimethylamine, while cooling with ice, we slowly added 0.5 ml of glacial acetic acid and 0.4 ml of 40% formalin. The solution was added to 0.44 g (2 mmole) of compound (II) in 4 ml of acetic acid, heated to 90°C, and kept for 6 h. The mixture was cooled, added to 100 ml of water, and made alkaline to pH 9. The precipitate was extracted with ether, the extracts were washed to a neutral reaction with water, dried with sodium sulfate, and filtered, the solvent was distilled, and compound (III) was obtained. The yield was quantitative; mp 178-179°C (from ether). UV spectrum (in alcohol), λ_{max} (log ε): 222 (4.38), 236 (4.41), 279 (4.75), 372 nm (3.86). Found, %: C 79.0; H 6.5; N 15.1. $C_{18}H_{17}N_3$. Calculated, %: C 78.6; H 6.2; N 15.3.

1-Formyl-3H-pyrrolo[2,3-c]acridine (IV). To 1.3 ml (6 mmole) of freshly distilled DMFA, which had been cooled to 0°C, we slowly added 0.4 ml (4.4 mmole) of phosphorus oxychloride. The mixture was stirred at room temperature for 1 h, a solution of 0.44 g (2 mmole) of 3H-pyrrolo[2,3-c]acridine in 8 ml of DMFA was added, and the mixture was heated to 80°C and kept for 7 h. It was then cooled, 50 ml of acetone was added and the precipitate was filtered off, washed with acetone, dissolved in 200 ml of hot water, and filtered. A 10% solution of sodium hydroxide was added to an alkaline reaction. The precipitated compound (IV) was filtered off. The yield was 0.32 g (64%); mp 152°C (from alcohol). IR spectrum (in Vaseline oil): 1665 (CO), 3380 cm^{-1} (NH). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.36), 234 (4.49), 269 (4.44), 372 nm (3.77). Found, %: C 77.6; H 3.9; N 11.1. $C_{16}H_{10}N_2O$. Calculated, %: C 78.0; H 4.1; N 11.4.

N-Acetyl-3H-pyrrolo[2,3-c]acridine (V). A 0.44-g sample of compound (II) (2 mmole) was boiled for 30 min with 4 ml of acetic anhydride and 0.2 g (2.5 mmole) of anhydrous sodium acetate. The solution was added to water, and the precipitate was filtered off, washed with water, and dried. The yield of (IV) was quantitative; mp 163°C (from ether). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.23), 244 (4.41), 270 (4.93), 350 (3.89), 368 nm (4.14). Found, %: C 78.1; H 4.6; N 10.9. $C_{17}H_{12}N_2O$. Calculated, %: C 78.5; H 4.6; N 10.8.

1-(4'-Nitrophenylazo)-3H-pyrrolo[2,3-c]acridine (VI). To a solution of 0.55 g (2.5 mmole) of compound (II) in 10 ml of dioxane and 4 ml of water at 2-3°C we added a solution of p-nitrobenzenediazonium chloride, neutralized to pH 7 and obtained by diazotization of 0.4 g (3 mmole) of p-nitroaniline by the usual method. The precipitate was filtered off, washed with acetone, dried, and crystallized from DMFA. The yield was 0.36 g (40%); mp 282-283°C (decomp., from DMFA). IR spectrum (Vaseline oil): 3360-3380 (NH), 1400 cm^{-1} (N=N). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.36), 236 (4.69), 286 (4.94), 385 (4.5), 410 nm (4.55). Found, %: C 68.7; H 3.6; N 18.8. $C_{21}H_{13}N_5O_2$. Calculated, %: C 68.7; H 3.6; N 19.0.

1-(4'-Chlorophenylazo)-3H-pyrrolo[2,3-c]acridine (VII). Compound (VII) was obtained by the method described above from 0.55 g (2.5 mmole) of compound (II) and 0.38 g (3 mmole) of p-chloroaniline. The precipitate obtained after azo coupling was washed with acetone, dried, and crystallized from alcohol. The yield was 0.28 g (32%); mp 272°C (decomp., from alcohol). IR spectrum (Vaseline oil): 3380-3390 (NH), 1410 cm^{-1} (N=N). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.59), 246 (4.64), 282 (4.92), 360 (4.41), 386 nm (4.45). Found, %: C 70.8; H 3.6; N 15.3. $C_{21}H_{13}ClN_4$. Calculated, %: C 70.7; H 3.7; N 15.7.

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2,4-DIPHENYL-3-AZAFLUORENE

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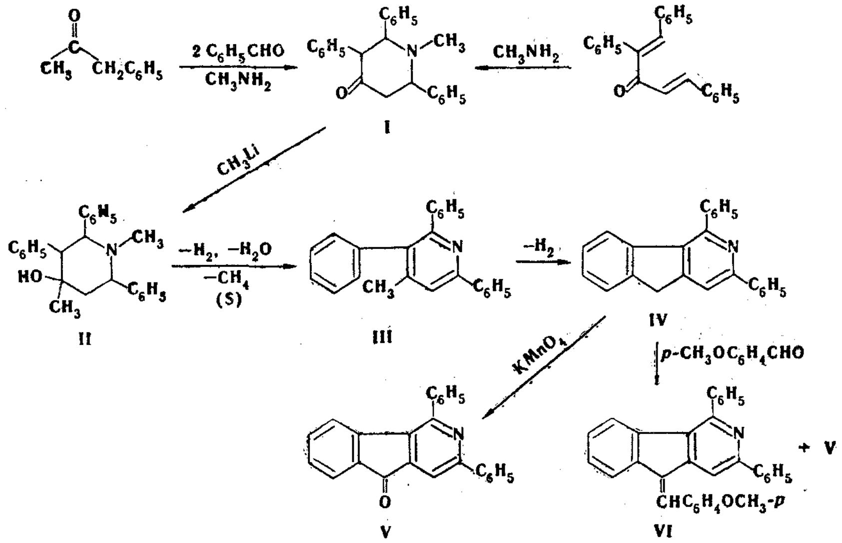
Among azafluorenes isomeric with respect to the position of the nitrogen atom, 3-azafluorenes are less well known than the others. Information about them is limited to reports on the synthesis of 3-azafluorenone by the pyrolysis of 3-o-carboxyphenylisonicotinic acid, obtained by oxidation of benzo[h]isoquinoline [1, 2], and on its synthesis from 3-phenylisonicotinoyl chloride [3]. The reduction of 3-azafluorenone to 3-azafluorene, which was only isolated in the form of the picrate [2, 3], and also the formation of a mixture of 1- and 3-azafluorenes by pyrolysis of phenyl-3-pyridyldiazomethane [2] have been described.

In order to obtain one of the first representatives of this heterocyclic system we used a scheme of three-stage synthesis, by which 3-methyl-2-azafluorene had previously been obtained in our laboratory from 1,2,5-trimethyl-4-piperidone [4]. As starting compound we used 1-methyl-2,3,6-triphenyl-4-piperidone (I), obtained by condensation of methyl benzyl ketone with benzaldehyde and methylation and also by reaction of 1,2,5-triphenyl-1,4-pentadien-3-one with methylamine.

From the piperidone (I) and methyllithium we obtained 1,4-dimethyl-2,3,6-triphenyl-4-piperidol (II). This tertiary γ-piperidol is formed as a single geometric isomer out of the eight possible isomers, and it evidently corresponds to the conformation with the equatorial orientation of the methyl group at C_4 and the phenyl radicals. When heated (200°C) with sulfur (by the method described in [5]), the piperidol (II) gave a high yield of 4-methyl-2,3,6-triphenylpyridine (III) as a result of simultaneously occurring dehydration, dehydrogenation,



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