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# CHEMISTRY OF INDOLE

## V. 1-Alkyl-5-(pyrid-4'-yl) indolines*

A. N. Kost, A. K. Sheinkman, and N. F. Kazarinova

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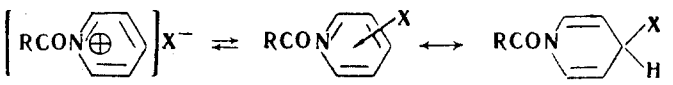
By treating 1-alkylindolines with 1-benzoylpyrylium salts in the presence of Lewis acids, good yields of 1-alkyl-5-(pyrid-4'-yl) indolines can be obtained. 1-alkyl-5-benzoylindolines are side products. The structures of the reaction products were demonstrated by UV and IR spectra, thin-layer chromatography, and dehydrogenation to the corresponding pyridylindoles.

As with 1-alkylpyridinium salts [2], a number of anions can be introduced into the ring of 1-acylpyridinium salts, the anion becoming bonded not ionically, but datively.



This kind of bond is rather labile, making it possible to use acylpyridinium salts for pyridylation [3]. In particular it was shown that dialkylaniline can be pyridylated by the action of such salts in the presence of aluminum chloride [3, 4]. A number of other Lewis acids have been tried for this reaction, and it has been found that anhydrous titanium tetrachloride gives the best results (Table 1).

Table 1

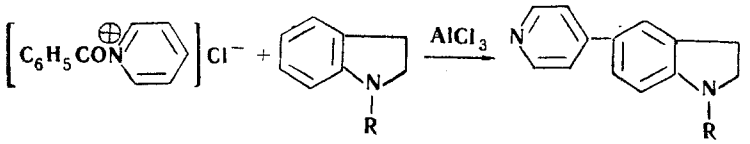
Comparison of Activities of Catalysts for Pyridylation of Dimethylaniline with 2-Benzoylpyridinium Chloride*

| Catalyst | Yield of 4-p-DMAPhP, % |
|---|---|
| $SnCl_4$ | 28 |
| $ZnCl_2$ (fused) | 34 |
| $SbCl_5$ | 37 |
| $BF_3 \cdot O(C_2H_5)_2$ | 39 |
| $AlCl_3$ | 56 |
| $TiCl_4$ | 69 |
| $ZnCl_2$ (crystalline) | 3 |
| $CuCl_2$ | Traces |
| CuCl | Traces |

* The results given are averages from 3 runs.

In all cases the reaction was carried out in one stage, without isolating the acylpyridinium salt. Previously [5] polarography of the reaction medium demonstrated the possibility of the existence of a benzoylpyridinium salt in pyridine solution as an active kinetically-independent intermediate compound. It is noteworthy that the least stable acylpyridinium chlorides (e.g., benzoylpyridinium chloride and the acylpyridinium salts of halogenoaliphatic anhydrides of higher molecular weight) give better yields in this reaction, than more stable compounds of that type (see [4], Table 2). It is of interest that exactly the same relationship has been found in the condensation of 1-acylpyridinium salts with aromatic aldehydes [6]. There, in the formation of acylpyridiniums, the shift sequence of the reagents is practically immaterial, unlike what obtains in the preparation of acylpyridinium salts, where it is extremely important [5]. Probably this is because the initially formed active intermediate complex is subsequently stabilized with formation of an acylpyridinium cation or a mixture of ketene and pyridine hydrochloride. Introduction of the Lewis acid stabilizes the acylpyridinium ion, which is also an active electrophilic agent.

The results obtained made it possible to extend the method to 1-alkylindolines, the cyclic analogs of dimethylanilines. It was shown that under ordinary conditions (benzoylpyridinium chloride and anhydrous aluminum chloride) these compounds (Table 2) are pyridylated at position 5 to give good yields, i.e., the γ position of the pyridine joins to the para position (with respect to the amino group) of the benzene ring of the indoline system (see Table 3).



* For the previous paper see [1].

Table 2

1-Alkylindolines

| Alkyl | Bp, °C (pressure, mm) | $n_D^{20}$ | Formula | Found, % | | | Calculated, % | | | Picrates (ex EtOH) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N | Mp, °C | Formula | N, % Found | N, % Calculated |
| $C_2H_5$ | 99—102 (8) | 1.5603 | $C_{10}H_{13}N$ | 81.19, 81.23 | 8.81, 8.78 | 9.79, 9.63 | 81.63 | 8.84 | 9.52 | 101—102 | $C_{10}H_{13}N \cdot C_6H_3N_3O_7$ | 14.92, 15.10 | 14,89 |
| $i$-$C_3H_7$ | 112—115 (10) | 1.5585 | $C_{11}H_{15}N$ | 81.51, 81.76, | 8.87, 9.04 | 8.97, 9.03 | 81.90 | 9.32 | 8.70 | 165—166 | $C_{11}H_{15}N \cdot C_6H_3N_3O_7$ | 14.41, 14.45 | 14,35 |
| $C_4H_9$ | 128—132 (12) | 1.5529 | $C_{12}H_{17}N$ | 82.10, 82.06 | 9.58, 9.53 | 7.98, 7.73 | 82.30 | 9.71 | 8.00 | 167—168 | $C_{12}H_{17}N \cdot C_6H_3N_3O_7$ | 14.07, 14.11 | 13,86 |
| $CH_2C_6H_5$* | 173—175 (8) | 1.6070 | $C_{15}H_{15}N$ | 86.13, 86.22 | 7.46, 7.41 | 6.79, 6.83 | 86.20 | 7.19 | 6.70 | 158—160 Decomposition | $C_{15}H_{15}N \cdot C_6H_3N_3O_7$ | 13.03, 12.89 | 12,55 |

* After standing for a long time in a refrigerator, the compound crystallized, mp 21.5°–22°; hydrochloride mp 144°–146° (ex acetone). Found: N 14.68, 14.58%. Calculated for $C_{15}H_{15}N \cdot HCl$: N 14.41%.

Table 3

1-Alkyl-5-(pyrid-4'-yl) indolines

| Alkyl | Mp, °C (recrystallization solvent) | UV spectrum (in EtOH) $\lambda_{max}$ mμ | UV spectrum (in EtOH) lg ε | Formula | Found, % C | Found, % H | Found, % N | Calculated, % C | Calculated, % H | Calculated, % N | Yield % | Picrates (ex EtOH) Mp, °C | Picrates (ex EtOH) Formula | N, % Found | N, % Calculated |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 129—129.5 (water) | 335 | 4.27 | $C_{14}H_{14}N_2$ | 79.89, 79.92 | 6.88, 6.71 | 12.75, 12.83 | 80.0 | 6.66 | 13.33 | 60 | 232—234 | $C_{14}H_{14}N_2 \cdot C_6H_3N_3O_7$ | 16.21, 16.11 | 15.94 |
| $C_2H_5$ | 75—76 (EtOH-water) | 340 | 4.30 | $C_{15}H_{16}N_2$ | 78.93, 78,73 | 7.15, 7.42 | 12.15, 12.23 | 80.03 | 7.14 | 12.50 | 58 | 199—200 | $C_{15}H_{16}N_2 \cdot C_6H_3N_3O_7$ | 15.26, 15.53 | 15.45 |
| $i$-$C_3H_7$ | 72—72,5 (PrOH-water) | 345 | 4.36 | $C_{16}H_{18}N_2$ | 81.12, 80.96 | 7.82, 7.75 | 11.58, 11.52 | 80.66 | 7.56 | 11.76 | 82 | 184—186 | $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$ | 14.75, 14.49 | 14.98 |
| $C_4H_9$ | 48—50, bp 220—230° (1mm) | 340 | 4.28 | $C_{17}H_{20}N_2$ | 80.65, 80.57 | 7.70, 7.73 | 11.08, 10.86 | 80.95 | 7.89 | 11.11 | 45 | 170—171 | $C_{17}H_{20}N_2 \cdot C_6H_3N_3O_7$ | 14.66, 14.89 | 14.55 |
| $CH_2C_6H_5$ | 125.5—126 (water) | 340 | 4.31 | $C_{20}H_{18}N_2$ | 84.12, 84.07 | 6.35, 6.28 | 9.72, 9.81 | 83.91 | 6.29 | 9.79 | 41 | 178—180 | $C_{20}H_{18}N_2 \cdot C_6H_3N_3O_7$ | 13.84, 13.73 | 13.58 |

Mobile thin-layer chromatography on alumina was used to analyze the products and choose the optimum reaction conditions. The solvents selected (Table 4) are such that $R_f$ s of the unreacted 1-alkylindolines differ sharply from those of the pyridylindolines (0.90 and 0.11–0.12). Further, all the pyridylated 1-alkylindolines fluoresced in ultraviolet light, so that they could easily be distinguished from the non-fluorescing starting indolines. In some cases the spots on

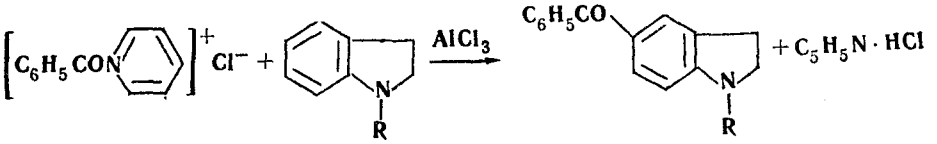
Table 4

$R_f$s of Indolines

| Compound | Solvent system | | | | | | |
|---|---|---|---|---|---|---|---|
| | $C_6H_6$ : $CHCl_3$ : 5 : 1 | $C_6H_6$ : $CHCl_3$ 1 : 1 | $C_6H_6$ : $n$-$C_6H_{12}$ : $CHCl_3$ 6 : 1 : 30 | : $n$-$C_6H_{12}$ : $CHCl_3$ 1 : 2 | $C_4H_8O_2$ : $n$-$C_6H_{12}$ 1 : 3 | $CHCl_3$ : $C_2H_5OH$ 99 : 1 | $C_6H_6$ : $C_4H_8O_2$ 1 : 1 |
| Indoline | 0.66 | 0.10 | 0.00 | 0.92 | 0.83 | 0.93 | 0.90 |
| 1-Methylindoline | 0.85 | 0.80 | 0.80 | 0.86 | 0.90 | 0.91 | 0.90 |
| 1-Ethylindoline | 0.89 | 0.88 | 0.88 | 0.87 | 0.90 | 0.92 | 0.90 |
| 1-Isopropylindoline | 0.86 | 0.87 | 0.89 | 0.88 | 0.92 | 0.92 | 0.94 |
| 1-Butylindoline | 0.92 | 0.90 | 0.93 | 0.89 | 0.87 | 0.94 | 0.89 |
| 1-Benzylindoline | 0.88 | 0.89 | 0.91 | 0.90 | 0.89 | 0.89 | 0.90 |
| 1-β-(Pyrid-4'-yl) ethylindoline | 0.17 | 0.18 | 0.38 | 0.24 | 0.55 | 0.56 | 0.83 |
| 1-Methyl-5-(pyrid-4'-yl) indoline | 0.10 | 0.11 | 0.23 | 0.12 | 0.43 | 0.41 | 0.77 |
| 1-Ethyl-5-(pyrid-4'-yl) indoline | 0.10 | 0.11 | 0.25 | 0.12 | 0.45 | 0.38 | 0.78 |
| 1-Isopropyl-5-(pyrid-4'-yl) indoline | 0.10 | 0.12 | 0.25 | 0.12 | 0.43 | 0.40 | 0.78 |
| 1-Butyl-5-(pyrid-4'-yl) indoline | 0.13 | 0.14 | 0.27 | 0.14 | 0.49 | 0.44 | 0.81 |
| 1-Benzyl-5-(pyrid-4'-yl) indoline | 0.11 | 0.14 | 0.25 | 0.15 | 0.42 | 0.46 | 0.82 |

the chromatograms were identified by preparative separation of the reaction products on an alumina column and isolation of pure compounds. In the other cases a combination of chromatography and visualizing was used. At 100° reaction was usually complete after 1 hr 30 min to 2 hr. When the reaction time was increased to 6 hr, the chromatogram spot corresponding to the starting indole disappeared, but there was considerable resinification.

Chromatography of the products made it possible to show that they contained traces of nonfluorescent 1-alkyl-5-benzoylindolines ($R_f$ 0.50–0.60 in the system benzene-hexane-$CHCl_3$ 6 : 1 : 30), these being formed by the side reaction



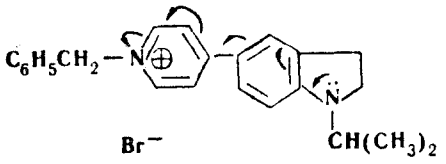

The 1-methyl-5-benzoylindoline isolated pure showed intense absorption in the 1640 $cm^{-1}$ region, characteristic of the carbonyl group. The UV spectrum showed intense absorption in the 265 mμ region, also characteristic of ketones. Thd compound does not form a picrate, no benzoic acid is detected after it has been boiled with hydrochloric acid, and a quantitative test for the carbonyl group is positive (precipitate with 2, 4-dinitrophenylhydrazine).

The case of C-alkylation of 1-acylpyridinium salts which we have observed is rare, although the abilities of these compounds to acylate readily at $NH_2$, SH, and OH groups are widely known [7].

In the present work, attempts were made to pyridylate, by means of acylpyridinium salts, nitrogen unsubstituted indoline and 1-acylindoline. All the attempts were unsuccessful, the final reaction products being pyridines, free indole and the acid whose chloride was used for preparing the acyl pyridiniums and acylindoles. The impossibility of pyridylating 1-acylindoles with acylpyridinium salts may be ascribed to insufficient nucleophilic nature of the p-carbon atom in the aromatic ring, due to drawing off of the lone electron pair by the amide carbonyl group, and this is in good accord with our view that the reaction is a typical electrophilic substitution [4]. In the actual reaction with the unsubstituted indole, the acylpyridinium salts behave not as pyridylating agents, but as acylating ones.

There is practically no doubt about the structure of the 1-alkyl-5-(pyrid-4'-yl) indolines. It is known that electrophilic reagents substitute 1-alkylindolines at position 5 only. Friedel-Crafts acylation with aluminum chloride takes place in that way [8]. Confirmation of structure was sought by determining the IR spectra of the 1-alkyl-5-pyrid-4'-yl-indolines. The absorption curves were found to be quite identical with that of 4-p-dialkylaminophenyl-

pyridine, of known structure (see fig.). The spectrum of 1-isopropyl-5-(pyrid-4'-yl)-indoline chlorobenzylate has an intense absorption band in the visible region (455 mμ, lg ε 4.20), analogous to that found with quaternary salts of 4-p-dialkylaminophenylpyridines [9]. This indicates that the pyridine nitrogen atom is quaternized by quaternary salt formation, and not the indoline one, since only then is charge delocalization by a conjugated chain possible, which is a necessary condition with ionoid compounds exhibiting color:

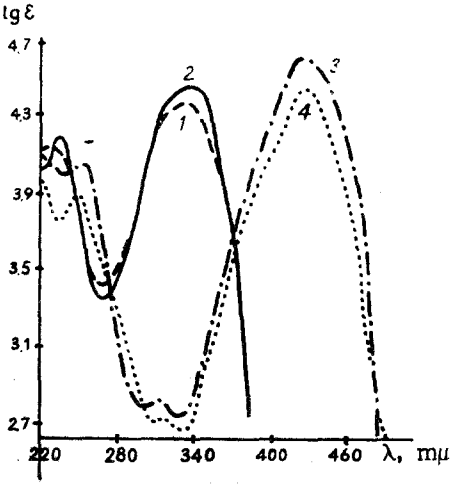



This also indicates that the nitrogen position of the pyridine ring is conjugated with respect to the amino group, i.e., supports the 1-alkyl-5-(pyrid-4'-yl) indolines structure.

Careful search, using various solvent systems, by chromatography on alumina or paper failed to reveal the presence of isomeric compounds.

The compounds prepared could be dehydrogenated to the corresponding pyridylindoles by boiling for several hours with cupric chloride in pyridine solution. In this particular case the generally used method of converting indoline derivatives to indoles using chloranil was inapplicable, as the latter formed stable complexes.

The UV spectrum of 1-methyl-5-(pyrid-4'-yl)indole showed the absorption characteristic of all indoles [10], though displaced somewhat towards the long wavelength region, at 265 mμ (lg ε 4.81) and 300 mμ (lg ε 4.40). A similar bathochromic shift was also observed with the UV spectra of 7-phenylindoles, e.g., 2-methyl-7-phenylindole $\lambda_{max}$ 243 mμ, lg ε 4.13 and 295 mμ, lg ε 4.06; 3-methyl-7-phenylindole $\lambda_{max}$ 240 mμ, lg ε 4.49 and 300 mμ, lg ε 4.13 [11]. Probably the considerable hypsochromic shift of the longwave absorption band with a pyridylindole as compared with a pyridylindoline (300 and 335 mμ) is due to elimination of the auxochrome, (i.e., the amino group of the indoline). In an indole the lone electron pair of the indoline nitrogen becomes common to the entire π-electron system. It is this which explains the change in color of the picrate from bright-red to pale-yellow on passing from pyridylindoline to pyridylindole, since with the latter the positive charge on the nitrogen of the pyridine ring remains in place.




UV spectra of 1-alkyl-5-(pyrid-4'-yl) indolines: 1) 1-Methyl-5-(pyrid-4'-yl) indoline; 2) 4-p-dimethylaminophenylpyridine; 3) 4-p-dimethylaminophenylpyridine bromobenzylate; 4) 1-methyl-5-(pyrid-4'-yl)indoline chlorobenzylate.

The fluorescent colors of pyridylindole (dark-blue glow) and pyridylindolines (greenish-blue) differ somewhat. Mobile thin-layer chromatography on alumina using several solvent systems led to separation of 1-methyl-5-(pyrid-4'-yl) indole and 1-methyl-5-(pyrid-4'-yl)-indoline, present in a mixture after dehydrogenation. It should be noted that generally it is extremely hard to separate this mixture by a chemical method, as the basicities of the two compounds, determined by the pyridine ring, are almost the same.

Pharmacological investigation of the pyridylindoles prepared (by I. B. Komissarov, Donetz Medical Institute) revealed compounds with considerable antiserotonin activity, and an antidepressive activity, which will form the subject of a separate communication.

## Experimental

Pyridylation of dimethylaniline with 1-benzoylpyridinium chloride, using various catalysts. As described previously [3], a reaction was carried out with 15.8 g dry pyridine, 14 g benzoyl chloride, and 12.1 g dimethylaniline in the presence of 0.11 mole (an equimolecular quantity based on the solvent pyridine + 0.1 mole per 1 mole benzoyl-

pyridinium salt) of various Friedel-Crafts catalysts (2 hr at 100°). As the yields of 4-p-dimethylaminophenylpyridine in this reaction are markedly dependent on possible fortuitous entrance of moisture, the reaction was carried out three times with each catalyst. The results are given in Table 1.

2,3-Dihydroindole. A solution of 34.8 g indole in 300 ml BuOH was mixed with 34 g amalgamated Zn dust and heated to boiling, then 400 ml 2:1 HCl was added dropwise in 4 hr. After 8–10 hr, when $H_2$ evolution had ceased, the water layer was separated off. The BuOH layer was washed a few times with 25–30 ml portions of 5% HCl, these extracts and the aqueous layer bulked, and the whole made alkaline with 40% alkali until the precipitate initially formed dissolved. The oily layer was separated off, the alkaline solution repeatedly extracted with ether, the ether extracts and the oily layer dried over anhydrous $K_2CO_3$, the ether distilled off, and the residue vacuum-distilled. Generally the yield of indoline was 10.5–12.5 g (26–34%), bp 108° (15 mm), 110° (17 mm), 130° (20 mm), $R_f$ 0.92 (benzene:hexane: $CHCl_3$ 6:1:30).*

1-Alkylindolines. A mixture of 11.9 g indoline and 10.6 g $Na_2CO_3$ was vigorously stirred and cooled, 0.1 mole of the appropriate alkyl halide dropped in gradually, and the whole then kept for 6 hr at 100°. After cooling the products were made alkaline with 20% alkali solution, the oily layer separated off, the alkaline solution carefully extracted with $CHCl_3$, the extracts and the oily layer bulked, dried over anhydrous $K_2CO_3$, the solvent distilled off, and the residue vacuum-distilled, to give, e.g., 1-methylindoline, bp 90°–95° (10 mm), in agreement with what is stated in the literature [8]. Other alkyl indoles were obtained in 50–60% yield, and their physical constants are given in Table 2.

1-Alkyl-5-(pyrid-4'-yl) indolines (Table 3). A mixture of 0.2 mole carefully dried pyridine and 0.1 mole freshly-distilled benzoyl chloride was kept for 1 hr 30 min to 2 hr in an oil bath at 100°. After cooling, 0.1 mole 1-alkylindoline was added, the mixture vigorously stirred and cooled in ice, and 0.1 mole anhydrous $AlCl_3$ added in portions. The reactants were stirred together for 2 hr at 100°, then decomposed with concentrated HCl, and steam-distilled. The residue in the distilling flask was made alkaline until the initial precipitate of $Al(OH)_3$ dissolved completely, and then steam distilled again. The pale brown amorphous solid in the flask was suction filtered off, boiled with HCl plus decolorizing charcoal, precipitated with $NH_4OH$, the precipitate washed a few times with hot water and dried, first on a porous plate, then in a vacuum. Table 3 gives the yields of impure 1-alkyl-5-(pyrid-4'-yl) indolines. For many purposes, further purification is unnecessary. Analytically pure specimens were obtained by recrystallizing from a very small amount of water. Silvery white plates, turning yellow in air, vacuum-distilling unchanged.

Picrates. These were bright-red. They were prepared by mixing ethanol solutions of 1-alkyl-5-(pyrid-4'-yl) indolines and picric acid. Purified by recrystallizing from EtOH.

1-Isopropyl-5-(pyrid-4'-yl) indoline chlorobenzylate. Prepared by boiling together 3 g 1-methylindoline and 1.6 g benzyl chloride in benzene. Yield 1.42 g (29.9%), orange crystals, mp 168°–170° (ex water and charcoal). UV spectrum: $\lambda_{max}$ 255, 455 mμ, lg ε 4.68, 4.21 (in EtOH). Found: N 7.47, 7.51; Cl 9.46, 9.34%. Calculated for $C_{23}H_{23}ClN_2$: N 7.68; Cl 9.73%.

1-Methyl-5-benzoylindoline. Part (1.5 g) of the crude 1-methyl-5-(pyrid-4'-yl)indoline, prepared as above, was carefully extracted with petrol ether in a Soxhlet apparatus, the solvent evaporated off, and the residue recrystallized from EtOH. Yield 0.33 g 1-methyl-5-benzoyl-indoline, white crystals, which did not form a picrate, mp 115°–116°; M cryoscopic 239.3, calculated 237; UV spectrum $\lambda_{max}$ 265 mμ, lg ε 4.07 (in EtOH). The IR spectrum had an intense absorption band at the 1642 $cm^{-1}$ region (in vaseline, IKS-14 instrument). Thin-layer chromatography on a plate, using alumina, gave one nonfluorescing spot, $R_f$ 0.59 (benzene:hexane:$CHCl_3$ 6:1:30); in the same system 1-methyl-5-(pyrid-4'-yl) indoline had $R_f$ 0.25, and the starting 1-methylindoline $R_f$ 0.89. Found: C 81.16, 81.07; H 6.33, 6.13; N 6.24, 6.19%. Calculated for $C_{16}H_{15}NO$: C 81.00; H 6.34; N 5.90%.

1-Methyl-5-(pyrid-4'-yl) indole. A solution of 1.05 g 1-methyl-5-(pyrid-4'-yl) indoline and 1.34 g anhydrous $CuCl_2$ in 10 ml pyridine, was refluxed on an oil bath for 15 hr, and the products then steam-distilled. The reddish-brown solid was treated with concentrated $NH_4OH$, then extracted with heptane in a Soxhlet apparatus. Evaporating off the heptane gave 0.5 g (47%) small white crystals, mp 200°–201°; UV spectrum: $\lambda_{max}$ 265, 300 mμ, lg ε 4.81, 4.40; $R_f$ 0.32 (benzene:hexane:$CHCl_3$ 6:1:30); in the same solvent system the starting 1-methyl-5-(pyrid-4'-yl) indoline had $R_f$ 0.25. It gave a positive Ehrlich test for an indole (crimson color with a HCl solution of p-dimethylaminobenzaldehyde). Found: C 80.56, 80.63; H 5.61, 5.83; N 13.15, 13.27%. Calculated for $C_{14}H_{12}N_2$: C 80.76; H 5.76; N 13.46%. Picrate pale yellow, mp 236°–237° (ex EtOH). Found: N 16.12%. Calculated for $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$: N 16.01%.

*Here and subsequently the results are for mobile thin-layer chromatography using alumina of grade II activity (Table 4).

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Lomonosov Moscow State University
Donetz Branch of the All-Union Scientific Research Institute
for Chemical Reagents and High-Purity Chemicals