Synthesis of 1,3-Disubstituted-5-oxo-7a-methyl-5,7a-dihydroindoles

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Cycloaddition and addition reactions of ethyl propiolate with a series of 1,3,5-substituted-2-amino-4-methylpyrroles to form, 1,3-disubstituted-5-oxo-7a-methyl-5,7a-dihydroindoles are described. High resolution mass spectral and pmr data are presented.

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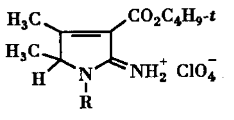
Introduction.

Historically, indole-3-carboxylic acids or their corresponding esters have been formed either from the Nenitzescu synthesis, though with a limited number of substitution patterns, or by esterification of the acid chloride obtained from the thermal elimination of indole-3-glyoxylyl chloride [1]. The 2-amino-3-acetylindoles, unsubstituted or substituted in 6-position, have also been prepared [2,3] *via* reduction of the 2-nitrophenylmalonic ester derivatives, though the 1-position must be substituted by an additional step. Aqueous hydrolysis at *p*H 3 of the vinyl ether function of 4,7-dihydro-5-methoxyindole [4] has yielded 5-oxo-4,5,6,7-tetrahydroindole but this compound has proven to be unstable. Additionally, 5-oxo-4,5-dihydroindoles may be formed by alkylation or acylation of the alkali metal salts of 5-hydroxyindole-3-carboxylic acid esters, accompanied by mono- or disubstitution in the 4-position [5].

In 1968, Blanton *et al.* [6] reported an anomalous behaviour for 2-amino-3-cyano-4,5-dimethylpyrrole as the result of protonation in the 5-position by trifluoroacetic acid. The same behaviour was reported [7] for 2-amino-3-cyano-4-methylpyrrole and 2-amino-3-*tert*-butoxycarbonyl-4-methylpyrrole. More recently, the immonium perchlorate salts of 1-*n*-butyl-2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrrole and the corresponding 1-isobutyl isomer were reported [8] to conform to the general structure **I**.



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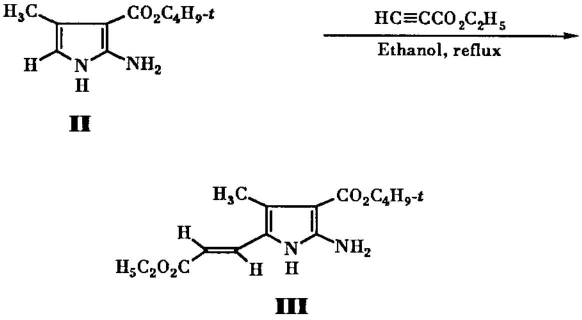
R = n-C_4H_9, i-C_4H_9

The anamolous protonation behaviour of the various 2-aminopyrroles would lead one to speculate that the 5-position in these heterocycles is electron-rich. This speculation was confirmed when Eger *et al.* [9] reported the synthesis of 1-methyl-2-amino-3-cyano-5-oxo-7a-methyl-5,7a-dihydroindole, a structure confirmed by X-ray crystallography. In the present work, 2-amino-3-*tert*-butoxycarbonyl-4-methylpyrrole (**II**) [7] was reacted with ethyl propiolate to yield the 1:1 Michael adduct, 2-amino-3-*tert*-butoxycarbonyl-4-methyl-5-([*E*]-2-ethoxycarbonylethenyl)pyrrole (**III**) (Scheme 1). When this reaction was carried out on various 1-substituted-2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles **IVa-h** [8] and the corresponding 1-benzyl-3-cyanopyrrole analog **IVi** [10] the ethyl ester addition products analogous to **III**, were not isolated. In these reactions the cyclized 1,3-disubstituted-2-amino-5-oxo-7a-methyl-5,7a-dihydroindoles **Va-i** were the products isolated and characterized (Scheme 2). These compounds were obtained in yields ranging from 15 to 70%.

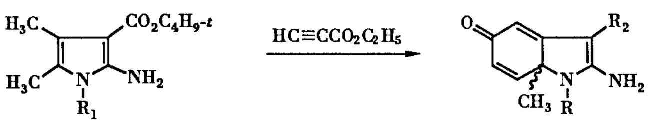
Scheme 1



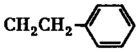
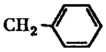
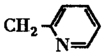
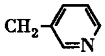
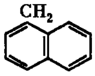
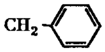
Proton magnetic resonance of these compounds was first order with the exception of an AB pattern seen in the CH_2 α to the 1-position in each compound, an example of nonequivalence we have seen previously with 1-benzyl-3-*tert*-butoxycarbonyl-4,5-dimethyl-2-(*N*-trifluoroacetyl-*N*-ethyl)aminopyrrole [11]. High resolution pmr was necessary due to: the relative insolubility of the compounds in all solvents except dimethyl sulfoxide and dimethylformamide, and the presence of overlapping peaks such as that between the *tert*-butyl CH_3 and 7a-methyl.

High resolution mass spectrometry reveals the base peak in compounds **Va-h** to be due to a McLafferty rearrangement of the *tert*-butyl ester **Va** (Scheme 3). There is also a loss of CH_3 from the 7a-position. This is followed by a loss of water (*ortho* effect), a loss normally seen in indole 2- and 7-carboxylic acids [12]. This is followed by decar-

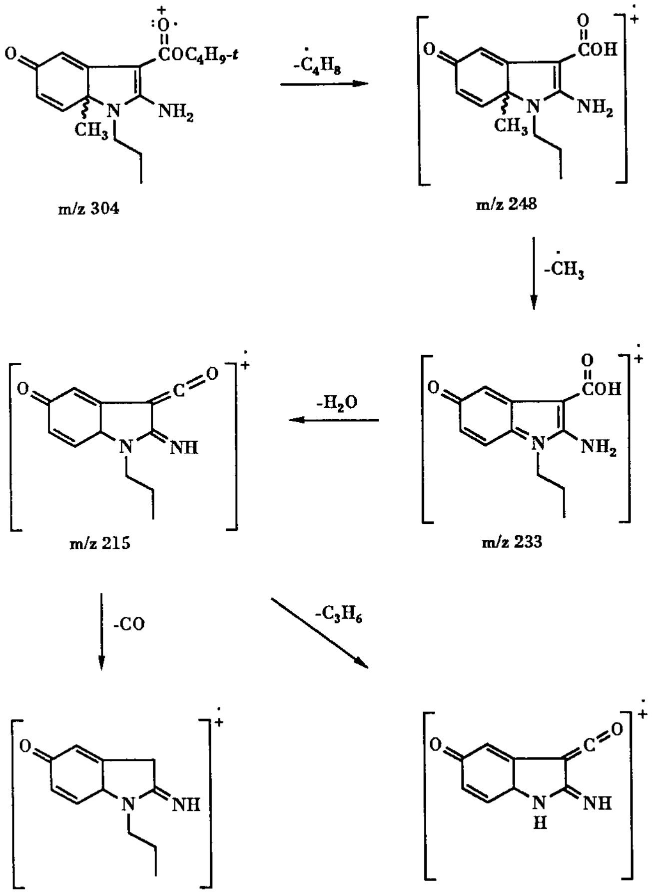
Scheme 2



IVa-i **Va-i**

No.	R_1	R_2
IV, Va	C_3H_7-*n*	$CO_2C_4H_9$-*t*
IV, Vb	$C_2H_4OCH_3$	$CO_2C_4H_9$-*t*
IV, Vc	$CH_2CH(OCH_3)_2$	$CO_2C_4H_9$-*t*
IV, Vd		$CO_2C_4H_9$-*t*
IV, Ve		$CO_2C_4H_9$-*t*
IV, Vf		$CO_2C_4H_9$-*t*
IV, Vg		$CO_2C_4H_9$-*t*
IV, Vh		$CO_2C_4H_9$-*t*
IV, Vi		CN

Scheme 3 (**Va**)



bonylation. Peaks appropriate to the loss of the 1-substituent were also observed.

EXPERIMENTAL

The melting points were determined on an Electrothermal apparatus and are uncorrected. The infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. The tlc was performed with Merck pre-coated silica gel plates, type 60. Mass spectra were performed using a heated direct insertion probe on a VG-70 SQ at 70 eV. The proton nmr spectra were obtained on a Brucker AM 500 FT-NMR spectrometer using default parameters (number of scans 32, acquisition time 3.277s, delay 1s, and a tip angle of 30 degrees) except as noted in the Experimental.

2-Amino-3-*tert*-butoxycarbonyl-4-methyl-5-([*E*]-2-ethoxycarbonylethenyl)pyrrole (**III**).

The 2-amino-3-*tert*-butoxycarbonyl-4-methylpyrrole (**II**) (0.01 mole, 1.96 g) [7] and ethyl propiolate (0.012 mole, 1.18 g) were added to a round-bottom flask containing 20 ml of absolute ethanol and stirred for 30 minutes at room temperature, then refluxed for an additional hour. While hot it was diluted with 10 ml of water then placed in the freezer overnight. The mustard-yellow crystals (2.0 g, 68%) were recrystallized from 2 parts methanol:1 part water followed by recrystallization from toluene, tlc R_f (ethyl acetate) 0.53, mp 199-200°; ir: ν NH, NH_2 3495, 3385, 3280 ν C=O 1660, 1620 cm^{-1}; pmr: δ 1.21 (t, 3H, OCH_2CH_3), 1.48 (s, 9H, *t*-butyl CH_3), 2.17 (s, 3H, 4-CH_3), 4.09 (q, 2H, OCH_2CH_3), 5.80 (d, 1H, H α to pyrrole, J_{trans} = 15.3), 6.14 (br s, 2H, 2-NH_2), 7.32 (d, 1H, H β to pyrrole, J_{trans} = 15.7), 10.63 ppm (br s, 1H, N_1-*H*).

Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 61.13; H, 7.54; N, 9.49.

General Procedure for the Reaction of 1-Substituted-2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles **IVa-h** with Ethyl Propiolate.

To a stirred solution of the 1-substituted-2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrrole **IVa-h** (20 mmoles) [8] in 20 ml of absolute ethanol was added ethyl propiolate (20 mmoles, 2.03 ml). The reaction mixture was stirred for 30 minutes at room temperature, then heated at reflux for an additional two hours. The mixture was cooled to 0° and the precipitate **Va-h** was collected by filtration.

1-Propyl-2-amino-3-*tert*-butoxycarbonyl-7a-methyl-5-oxo-5,7a-dihydroindole (**Va**).

This compound was obtained as bright yellow needles (2 parts methanol:1 part water) in 38% yield, tlc R_f (19 parts acetone:1 part methanol) 0.63, mp 248-249° dec; ir: ν NH_2 3330, 3290, ν C=O 1650, 1620, ν C-O 1245, 1135 cm^{-1}; pmr: δ 0.88 (t, 3H, $NCH_2CH_2CH_3$), 1.47 (s, 3H, 7a-CH_3), 1.48 (br s, 11H, *t*-butyl CH_3 & $NCH_2CH_2CH_3$), 3.37 (m, 2H, $NCH_2CH_2CH_3$), 5.74 (d, 1H, 4-*H*, J = 1.6 Hz), 5.86 (dd, 1H, 6-*H*, J = 9.9, 1.8 Hz), 7.12 (d, 1H, 7-*H*, J = 9.9 Hz), 7.87 ppm (br s, 2H, 2-NH_2); ms: (m/z) 304.1781, error 1.9 ppm (M^+), 248.1162, base peak, error 0.4 ppm (M^+-C_4H_8), 233.0923, error 1.4 ppm (M^+-C_4H_8 & CH_3), 215.0826, error 2.5 ppm (M^+-C_4H_8 & CH_3 & H_2O), 187 (M^+-C_4H_8 & CH_3 & H_2O & CO), 173 (M^+-C_4H_8 & CH_3 & H_2O & CO & C_3H_6).

Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.22; H, 8.01; N, 9.20.

1-(2-Methoxyethyl)-2-amino-3-*tert*-butoxycarbonyl-7a-methyl-5-oxo-5,7a-dihydroindole (**Vb**).

This compound was obtained by concentrating the reaction mixture *in vacuo* and dissolving in boiling hexanes (150 ml). Crystals are obtained at 0° and these are then recrystallized from ethyl acetate (100 ml) at 0°. Bright yellow crystals are obtained in 70% yield, tlc R_f (19 parts acetone:1 part methanol) 0.72, mp 194° dec; ir: ν NH_2 3325, ν C=O 1655, 1625, ν C-O 1245 cm^{-1}; pmr: δ 1.48 (s, 3H, 7a-C*H*$_3$), 1.49 (s, 9H, *t*-butyl C*H*$_3$), 3.27 (s, 3H, OC*H*$_3$), 3.42 (t, 2H, NCH_2C*H*$_2$$OCH_3$, J = 10.7 Hz), 3.62 (m, 2H, NC*H*$_2$$CH_2OCH_3$), 5.75 (d, 1H, 4-*H*, J = 1.6 Hz), 5.83 (dd, 1H, 6-*H*, J = 9.9, 1.8 Hz), 7.12 (d, 1H, 7-*H*, J = 9.9 Hz), 7.78 ppm (br s, 2H, 2-N*H*$_2$); ms: (m/z) 320.1732, error 1.3 ppm (M^+), 264, base peak (M^+-C_4H_8), 249 (M^+-C_4H_8 & CH_3), 231 (M^+-C_4H_8 & CH_3 & H_2O).

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.74; H, 7.50; N, 8.72.

1-(2,2-Dimethoxyethyl)-2-amino-3-*tert*-butoxycarbonyl-7a-methyl-5-oxo-5,7a-dihydroindole (**Vc**).

This compound was obtained as bright yellow prisms (ethyl acetate) in 48% yield, tlc R_f (19 parts acetone:1 part methanol) 0.63, mp 203-205° dec; ir: ν NH_2 3360, 3280, ν C=O 1650, 1620, ν C-O 1250, 1145 cm^{-1}; pmr: δ 1.47 (s, 3H, 7a-C*H*$_3$), 1.49 (s, 9H, *t*-butyl C*H*$_3$), 3.56 (center of AB multiplet, 2H, C*H*$_2$$CH(OCH_3)_2$), 4.44 (t, 1H, CH_2C*H*$(OCH_3)_2$, J = 5.3 Hz), 3.35 (d, 6H, CH_2CH (OC*H*$_3$)$_2$), 5.76 (d, 1H, 4-*H*, J = 1.6 Hz), 5.84 (dd, 1H, 6-*H*, J = 9.9, 1.8 Hz), 7.12 (d, 1H, 7-*H*, J = 10.0 Hz), 7.79 ppm (br s, 2H, 2-N*H*$_2$); ms (m/z) 350.1833, error 2.6 ppm (M^+), 294, base peak (M^+-C_4H_8), 279 (M^+-C_4H_8 & CH_3).

Anal. Calcd. for $C_{18}H_{26}N_2O_5$: C, 61.69; H, 7.47; N, 7.99. Found: C, 61.62; H, 7.51; N, 7.94.

1-(2-Phenylethyl)-2-amino-3-*tert*-butoxycarbonyl-7a-methyl-5-oxo-5,7a-dihydroindole (**Vd**).

This compound was obtained as bright yellow crystals (2 parts methanol:1 part water) in 51% yield, tlc R_f (19 parts acetone:1 part methanol) 0.68, mp 225-226° dec; ir: ν NH_2 3340, 3300, ν C=O 1650, 1615, ν C-O 1245, 1135 cm^{-1}; pmr: δ 1.47 (s, 3H, 7a-C*H*$_3$), 1.50 (s, 9H, *t*-butyl C*H*$_3$), 2.74 (br m, 1H, CH_2C*H*H'-phenyl), 2.83 (br m, 1H, CH_2CH*H'*-phenyl), 3.61 (br m, 1H, C*H*H'CH_2-phenyl), 3.73 (br m, 1H, CH*H'*CH_2-phenyl), 5.71 (d, 1H, 4-*H*, J = 1.7 Hz), 5.74 (dd, 1H, 6-*H*, J = 2.6, 1.5 Hz), 6.84 (d, 1H, 7-*H*, J = 9.8 Hz), 7.21-7.36 (m, 5H, phenyl protons), 7.99 ppm (br s, 2H, 2-N*H*$_2$); ms: (m/z) 366.1938, error 1.4 ppm (M^+), 310, base peak (M^+-C_4H_8), 295 (M^+-C_4H_8 & CH_3), 277 (M^+-C_4H_8 & CH_3 & H_2O).

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65. Found: C, 72.09; H, 7.16; N, 7.63.

1-Benzyl-2-amino-3-*tert*-butoxycarbonyl-7a-methyl-5-oxo-5,7a-dihydroindole (**Ve**).

This compound was obtained as bright yellow crystals (ethanol) in 34% yield, tlc R_f (19 parts acetone:1 part methanol) 0.57, mp 258-259° dec; ir: ν NH_2 3340, 3280, ν C=O 1650, 1615, ν C-O 1250, 1145 cm^{-1}; pmr: δ 1.51 (br s, 12H, *t*-butyl C*H*$_3$ & 7a-C*H*$_3$), 4.84 (center of AB multiplet, 2H, C*H*$_2$-phenyl), 5.74 (dd, 1H, 6-*H*, J = 9.8, 1.7 Hz), 5.79 (d, 1H, 4-*H*, J = 1.6 Hz), 6.76 (d, 1H, 7-*H*, J = 9.8 Hz), 7.18-7.38 (m, 5H, phenyl protons), 7.99 ppm (br s, 2H, 2-N*H*$_2$); ms: (m/z) 352.1784, error 0.9 ppm (M^+), 296, base peak (M^+-C_4H_8), 281 (M^+-C_4H_8 & CH_3), 263 (M^+-C_4H_8 & CH_3 & H_2O), 235 (M^+-C_4H_8 & CH_3 & H_2O & CO).

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot 0.25H_2O$: C, 70.66; H, 6.93; N, 7.85. Found: C, 70.68; H, 6.93; N, 7.82.

1-(2-Pyridylmethyl)-2-amino-3-*tert*-butoxycarbonyl-5-oxo-7a-methyl-5,7a-dihydroindole (**Vf**).

The compound was obtained as yellow crystals (ethyl acetate) in 55% yield, tlc R_f (19 parts acetone:1 part methanol) 0.46, mp 255-257° dec; ir: ν NH_2 3340, 3290, ν C=O 1655, 1615, ν C-O 1245, 1140 cm^{-1}; pmr: δ 1.50 (s, 9H, *t*-butyl C*H*$_3$), 1.52 (s, 3H, 7a-C*H*$_3$), 4.89 (center of AB multiplet, 2H, C*H*$_2$-pyridyl), 5.77 (d, 1H, 4-*H*, J = 1.7 Hz), 5.80 (dd, 1H, 6-*H*, J = 4.3, 1.6 Hz), 6.84 (d, 1H, 7-*H*, J = 9.8 Hz), 8.10 (br s, 2H, 2-N*H*$_2$), 7.37-7.40, 7.52-7.54, 8.46-8.49 ppm (4m, 4H, pyridyl protons); ms: (m/z) 353.1730, error 2.5 ppm (M^+), 297, base peak (M^+-C_4H_8), 282 (M^+-C_4H_8 & CH_3), 264 (M^+-C_4H_8 & CH_3 & H_2O), 236 (M^+-C_4H_8 & CH_3 & H_2O & CO).

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.88; H, 6.61; N, 11.84.

1-(3-Pyridylmethyl)-2-amino-3-*tert*-butoxycarbonyl-5-oxo-7a-methyl-5,7a-dihydroindole (**Vg**).

This compound was obtained as yellow crystals (16%) after trituration in 1 part toluene:1 part hexanes followed by filtration. The crude product was then recrystallized from acetone, tlc R_f (19 parts acetone:1 part methanol) 0.40, mp 254° dec; ir: ν NH_2 3330, 3275 ν C=O 1650, 1615 cm^{-1}; pmr: δ 1.51 (s, 9H, *t*-butyl C*H*$_3$), 1.52 (s, 3H, 7a-C*H*$_3$), 4.88 (center of AB multiplet, 2H, C*H*$_2$-pyridyl), 5.78 (d, 1H, 4-*H*, J = 1.7 Hz), 5.80 (dd, 1H, 6-*H*, J = 4.6, 1.7 Hz), 6.84 (d, 1H, 7-*H*, J = 9.8 Hz), 8.02 (br s, 2H, 2-N*H*$_2$), 7.37-7.40, 7.53-7.54, 8.46-8.49 ppm (4m, 4H, pyridyl protons); ms: (m/z) 353.1736, error 0.8 ppm (M^+), 297, base peak (M^+-C_4H_8).

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.96; H, 6.62; N, 11.79.

1-(1-Napthylmethyl)-2-amino-3-*tert*-butoxycarbonyl-5-oxo-7a-methyl-5,7a-dihydroindole (**Vh**).

This compound was obtained as bright yellow crystals (ethyl acetate) in 58% yield, tlc R_f (19 parts acetone:1 part methanol) 0.53, mp 278-280° dec; ir: ν NH_2 3350, 3280, ν C=O 1690, 1615, ν C-O 1195, 1165 cm^{-1}; pmr: (number of scans 256) δ 1.53 (s, 9H, *t*-butyl C*H*$_3$), 1.64 (s, 3H, 7a-C*H*$_3$), 5.31 (center of AB multiplet, 2H, C*H*$_2$-naphthyl), 5.72 (dd, 1H, 6-*H*, J = 9.8, 1.8 Hz), 5.85 (d, 1H, 4-*H*, J = 1.6 Hz), 6.66 (d, 1H, 7-*H*, J = 9.9 Hz), 6.9-8.12 (m, 7H, naphthyl protons), 8.0 ppm (br s, 2H, 2-N*H*$_2$); ms: (m/z) 402.1947, error 1.0 ppm (M^+), 346, base peak (M^+-C_4H_8).

Anal. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.43; H, 6.57; N, 6.95.

1-Benzyl-2-amino-3-cyano-5-oxo-7a-methyl-5,7a-dihydroindole (**Vi**).

The 2-amino-3-cyano-4,5-dimethylpyrrole (**IVi**) [10] (0.02 mole, 4.5 g) and ethyl propiolate (0.022 mole, 2.18 g) were added to a round-bottom flask containing 30 ml of absolute ethanol and stirred for 30 minutes at room temperature, then refluxed for an additional hour. The reaction mixture was then diluted with 30 ml of water and cooled to 0°. The black gummy residue was recrystallized twice (ethyl acetate) to yield (0.8 g, 15%) bright yellow crystals, tlc R_f (19 parts acetone:1 part methanol) 0.60, mp 274-275° dec; ir: ν NH_2 3410, 3305, ν C=O 1620 cm^{-1}; pmr: δ

1.54 (s, 3H, 7a-CH_3), 4.81 (center of AB multiplet, 2H, CH_2-phenyl), 5.29 (d, 1H, 4-*H*, J = 1.7 Hz), 5.75 (dd, 1H, 6-*H*, J = 9.8, 1.7 Hz), 6.74 (d, 1H, 7-*H*, J = 9.9 Hz), 7.17-7.38 (m, 5H, phenyl protons), 8.11 ppm (br s, 2H, 2-NH_2); ms: (m/z) 277.1214, error 0.4 ppm (M^+), 91, base peak (benzyl$^+$).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.72; H, 5.46; N, 15.19.

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