Synthetic Studies on Pyrroloquinolines. II. Studies on the Syntheses and Chemical Properties of 1*H*-Pyrrolo[2,3-*b*]quinolines

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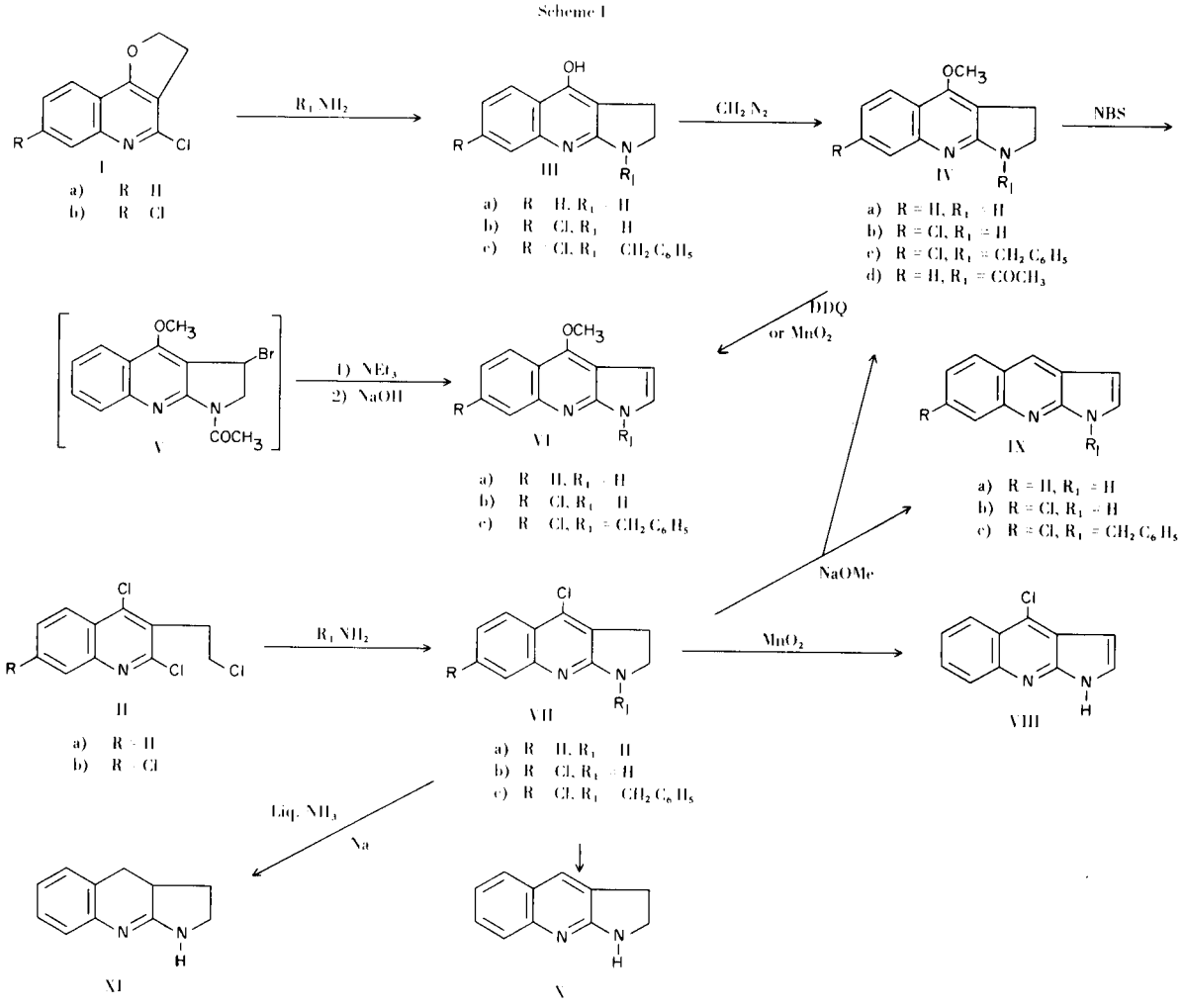
This paper describes the syntheses and the properties of 1*H*-pyrrolo[2,3-*b*]quinolines derived from 2,3-dihydrofuro[3,2-*c*]quinolines or 3-(β-chloroethyl)-2,4-dichloroquinolines. The discrepancy on the physical data of 1*H*-pyrrolo[2,3-*b*]quinoline between our product and Perkin's previously reported product is also discussed.

We previously reported (1) the preparation of a series of compounds containing the 2,3-dihydro-1*H*-pyrrolo-[2,3-*b*]quinoline ring system by the action of ammonia or primary amines on 4-chloro-2,3-dihydrofuro[3,2-*c*]quinolines (I) or 3-(β-chloroethyl)-2,4-dichloroquinolines (II). As an extension of this investigation, we now wish to describe our studies on the syntheses of 1*H*-pyrrolo-[2,3-*b*]quinolines possessing a fully aromatized system.

Scheme I



As our first object, dehydrogenation of the 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolines was investigated. Bromination of 1-acetyl-4-methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-quinoline (IVd) with *N*-bromosuccinimide gave the unstable 3-bromide (V) which gave a fair yield of 4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (VIa) upon treatment with boiling triethyl amine followed by deacetylation with dilute sodium hydroxide. The structure of VIa was confirmed by means of the elemental analyses and nmr spectrum which exhibited the presence of the two newly formed protons at 2.50 and 3.30 τ. This compound is referred to as an aza-analogue of dictamnine, a member of the furoquinoline alkaloids (2), and showed a uv spectrum closely similar to that of the alkaloid.

An alternative method using manganese dioxide was found effective for the dehydrogenation of the 2,3-dihydro compounds not containing a substituent at the 1-position (4). On the other hand, the 1-benzyl derivative (IVc) was converted into the corresponding pyrroloquinoline (VIc) by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Replacement of the chlorine atom at the 4-position of the dihydro compound (VIIb) by methoxyl group was quite sluggish when sodium methoxide was used in boiling methanol and, in order to accelerate the reaction, heating in a sealed tube at 110-120° was necessary. Of those three products isolated from the reaction mixture, the first compound, obtained in 40% yield, was the expected 4-methoxy derivative (IVb). The second product, separated in a trace, was identical with the 4-hydroxy compound (IIIb) (1), the amount of which increased suddenly with a decreasing of IVb when the reaction temperature exceeded 130°. The last compound, obtained in 40% yield, was assigned the structure, unexpectedly, 7-chloro-1*H*-pyrrolo[2,3-*b*]quinoline (IXb) based on its mass and nmr spectral data. When this reaction was carried out in a dipolar aprotic solvent such as *N*,*N*-dimethylformamide or dimethyl sulfoxide instead of methanol, smooth elimination of hydrogen chloride took place even under atmospheric pressure, yielding IXb almost quantitatively. Although the 1-benzyl-4-chloro derivative (VIIc) was likewise subjected to this noval dehydrochlorination, the dihydro compound (X) having no chlorine atom at the 4-position was not affected under the same reaction conditions.

This reaction presumably involves the metallation of $N_{(a)}$ by sodium methoxide with an accompanying mesomeric migration of the lone pair-electrons on $N_{(b)}$ at the first stage as shown in Scheme II.

In this connection, Yakhontov *et al.* have reported an anomalous dehydrogenation of 7-azaindolines under the conditions of the Birch reduction to give 7-azaindoles (5). Application of this procedure to our 2,3-dihydropyrroloquinoline system only gave a hydrogenated product (XI) from VIIa. The gross structure of XI was proposed from consideration of its mass [m/e = 172 (M^+)] and nmr (7 aliphatic and 4 aromatic protons) data. Ultimately, the position of the double bond was determined by its analogy in the uv spectrum with that of 2-aminoindolenine (6).

However, the recorded melting point and solubility of Perkin and Robinson's product (XIII) (7), synthesized along the pathway shown in Scheme III were not consistent with those of our's (IXa). The results of a re-investigation of their method strongly suggested the alternation of their structural formulae (XII), (XIII) and (XIV), to (XII′), (XIII′) and (XIV′), respectively, on the basis of the appearance of a nitrile stretching band in the ir spectra in addition to the close similarity of the uv spectrum of XIII′ with that of quinoline itself.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded with a JASCO IR-E spectrometer as nujol mulls. The uv spectra were determined using a Hitachi EPS-2U spectrometer. The nmr spectra were obtained with a JEOL JNM-MH-60 spectrometer with tetramethylsilane as the internal standard. The mass spectra were measured with a Hitachi RMS-4 spectrometer.

1-Acetyl-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (IVd).

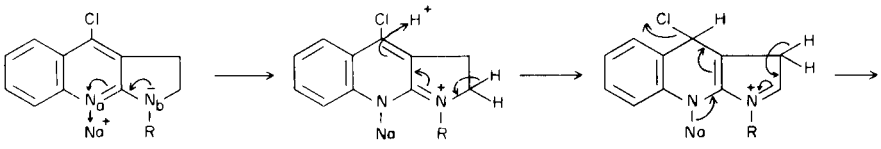
A solution of 3.5 g. of IVa in 3 ml. of acetic anhydride and 2 ml. of glacial acetic acid was warmed at 70-75° for 2.5 hours. The solvent was then removed under vacuum and the residue was triturated with a small amount of ether. The resulting white solid was recrystallized from chloroform to give 3.0 g. (72%) of IVd as colorless prisms, m.p. 118-119°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.26; H, 5.66; N, 11.80.

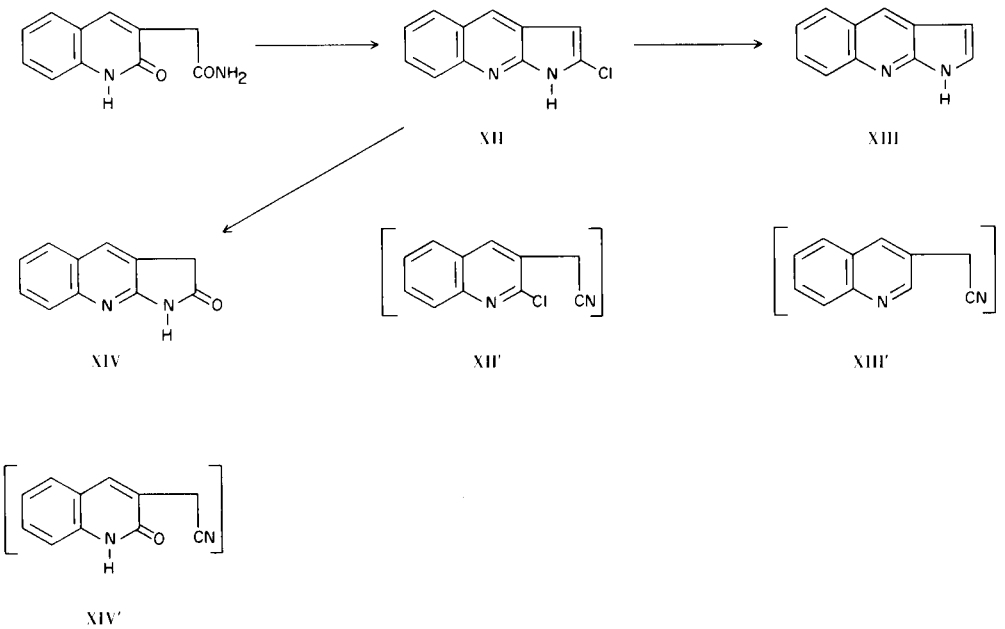
4-Methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (VIa).

A suspension of 2.9 g. (0.012 mole) of IVd, 2.15 g. (0.013 mole) of *N*-bromosuccinimide and 0.1 g. of benzoyl peroxide in 100 ml. of carbon tetrachloride was refluxed for one hour. The succinimide was filtered and the mother liquor was evaporated to dryness. The residue was dissolved in 5 ml. of triethyl amine and

Scheme II



Scheme III



the solution was refluxed for 6 hours. Excessive triethyl amine was evaporated *in vacuo*, and the residue was extracted with chloroform. After drying and distilling the solvent, a solution of 1.5 ml. of 10% sodium hydroxide in 3 ml. of methanol was added to the residue and the mixture was heated at 60-65° for 30 minutes. The solution was diluted with water and the crystals which separated were collected, washed with acetone and recrystallized from chloroform to yield 0.89 g. of VIa as colorless rhombs, m.p. 231-233°; ν max (nujol) cm^{-1}: 1630, 1610, 1580; λ max (ethanol) mμ (log. ϵ): 246 (4.94), 346 (3.88); nmr τ (deuterio chloroform-trifluoroacetic acid); 5.45 (3H, singlet, $-OCH_3$), 3.18 (1H, doublet, J = 4 Hz, C_3-H), 2.77 (1H, singlet, J = 4 Hz, C_2-H), 2.7-1.82 (4H).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.68; H, 4.98; N, 14.03.

Manganese Dioxide Dehydrogenation of 7-Chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (IVb).

A suspension of 0.24 g. of (IVb) and 0.87 g. of manganese dioxide in 20 ml. of chloroform was stirred at room temperature for 24 hours. The reaction mixture was then filtered and the mother liquor was concentrated to about ½ volume by evaporation under reduced pressure causing crystallization of 0.075 g. of 7-chloro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (VIb) as colorless rhombs, m.p. 242-243°; nmr τ (DMSO-d_6): 6.72 (3H, singlet, OCH_3), 3.15 (1H, doublet, J = 4 Hz, C_3-H), 2.84 (1H, quartet, J = 9, 2Hz, C_6-H), 2.52 (1H, doublet, J = 4 Hz, C_2-H), 2.27 (1H, doublet, J = 2 Hz, C_8-H), 1.90 (1H, doublet, J = 9 Hz, C_5-H).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.98; H, 3.86; N, 12.04; Cl, 15.23. Found: C, 61.90; H, 3.90; N, 12.19; Cl, 15.54.

DDQ Dehydrogenation of 1-Benzyl-7-chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (IVc).

A solution containing 0.34 g. of (IVc) and 0.43 g. of DDQ in 30 ml. of benzene was refluxed for 6 hours. After cooling, the separated solid was filtered and the filtrate was washed with 10% aqueous sodium hydroxide, water and dried over anhydrous sodium sulfate. After evaporating the solvent the residue was dissolved in chloroform and the solution was passed through a short alumina column to remove a highly colored impurity. The eluent was purified by recrystallization using methanol to afford 0.10 g. (29.4%) of 1-benzyl-7-chloro-4-methoxy-1*H*-pyrrolo[2,3-*b*]-quinoline (VIc) as colorless prisms, m.p. 100-102°; nmr τ (deuterio chloroform); 6.58 (3H, singlet, $-OCH_3$), 4.55 (2H, singlet, benzyl-CH_2-), 3.27 (1H, doublet, J = 4 Hz, C_3-H), 2.91 (1H, doublet, J = 4 Hz, C_2-H), 2.85-1.85 (8H).

Anal. Calcd. for $C_{19}H_{15}ClN_2O.\frac{1}{2}CH_3OH$: C, 69.10; H, 5.06; N, 8.27. Found: C, 69.37; H, 4.77; N, 8.28.

4-Chloro-1*H*-pyrrolo[2,3-*b*]quinoline (VIII).

A suspension of 7.0 g. of 4-chloro-2,3-dihydro-1*H*-pyrrolo-[2,3-*b*]quinoline (VIIa) and 70.0 g. of activated manganese dioxide (8) in 700 ml. of chloroform was stirred for 72 hours at room temperature. After filtering the inorganic material, the filtrate was concentrated to about 1/3 volume and was set aside for 16 hours. Separated crystals were collected and recrystallized from chloroform to give 4.4 g. (63%) of VIII as colorless rhombs, m.p. 236-238° dec.; the hydrochloride m.p. 238° dec.; λ max (ethanol) mμ (log. ϵ): 265 (4.94), 316 (3.88) (sh.), 332 (4.09).

Anal. Calcd. for $C_{11}H_7ClN_2$: C, 65.24; H, 3.48; N, 13.83. Found: C, 65.12; H, 3.33; N, 13.97.

Reaction of VIIa with Sodium Methoxide in Dimethyl Sulfoxide.

A mixture of 2.05 g. (0.01 mole) of VIIa, 5.44 g. (0.08 mole) of sodium methoxide and 40 ml. of dimethyl sulfoxide was heated at 100° for one hour. After cooling, 200 ml. of water was added to the reaction mixture and the deposited solid was collected and recrystallized from methanol to give 1.4 g. (83.3%) of 1*H*-pyrrolo[2,3-*b*]quinoline (IXa) as colorless rhombs, m.p. 209-210° dec.; the picrate m.p. 238-240° dec.; nmr τ (deuteriochloroform); 3.30 (1H, doublet, J = 4 Hz, C_3-H), 1.75-2.70 (5H), 1.50 (1H, singlet, C_5-H).

Anal. Calcd. for $C_{11}H_8N_2 \cdot C_6H_3N_3O_7$: C, 51.39; H, 2.79;

N, 17.62. Found: C, 51.71; H, 2.85; N, 17.76.

7-Chloro-1*H*-pyrrolo[2,3-*b*]quinoline (IXb).

By using the same procedure described above, 4,7-dichloro-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinoline (VIIb) was converted into IXb quantitatively; m.p. 243-245° dec. (DMF); nmr τ (DMSO-d_6): 3.40 (1H, quartet, J = 4, 1.5 Hz, C_3-H), 2.66 (1H, quartet, J = 9, 2 Hz, C_6-H), 2.18 (1H, quartet, J = 4, 1.5 Hz, C_2-H), 2.05 (1H, doublet, J = 2 Hz, C_8-H), 2.00 (1H, doublet, J = 9 Hz, C_5-H), 1.52 (1H, singlet, C_4-H).

Anal. Calcd. for $C_{11}H_7ClN_2$: C, 65.20; H, 3.48; N, 13.83. Found: C, 65.41; H, 3.45; N, 13.77.

Reaction of VIIb with Sodium Methoxide in Methanol.

A mixture of 0.48 g. of VIIb, 1.08 g. sodium methoxide and 15 ml. of methanol was heated at 100-120° for 8 hours in a sealed tube. The solvent was then evaporated *in vacuo* and the residue was taken up in chloroform. After evaporating the solvent, the residue was purified by column chromatography on silica using ethyl acetate. From the first eluent 0.17 g. (41.3%) of IXb was obtained. The second fraction gave 0.20 g. (42.7%) of 7-chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (IVb) as colorless rhombs, m.p. 228-230° dec. (methanol). This compound was identified with an authentic specimen reported in the previous paper by the mixed melting point test and the comparison of the ir spectra.

1-Benzyl-7-chloro-1*H*-pyrrolo[2,3-*b*]quinoline (IXc).

A mixture of 0.33 g. of VIIc, 0.54 g. of sodium methoxide and 4 ml. of diglyme was heated at 120° for 17 hours. The reaction mixture was distilled *in vacuo* and the residue was taken up in benzene. After evaporating the solvent, the residue was purified by preparative thin-layer chromatography on silica gel using ethyl acetate. From the upper layer 0.15 g. (51.3%) of IXc was obtained m.p. 103-105°; the picrate m.p. 194-195° dec. (methanol).

Anal. Calcd. for $C_{18}H_{13}ClN_2 \cdot C_6H_3N_3O_7$: C, 55.24; H, 3.09; N, 13.42. Found: C, 55.56; H, 3.13; N, 13.89.

Elution of the lower band gave 0.057 g. (18%) of 1-benzyl-7-chloro-2,3-dihydro-4-methoxy-1*H*-pyrrolo[2,3-*b*]quinoline (IVc) as colorless plates, m.p. 123-124°; the hydrochloride m.p. 207-208° dec. (methanol). This compound was identical with an authentic specimen reported in the previous paper (1) by comparison of the ir spectra.

2,3-Dihydro-1*H*-pyrrolo[2,3-*b*]quinoline (X).

A solution of 1.05 g. of VIIa in 30 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.3 g. of 10% palladium on carbon. About 116 ml. of hydrogen was absorbed during 2 hours and the absorption stopped. The catalyst was filtered and the filtrate was distilled *in vacuo* to leave a solid residue. This was treated with 1% aqueous sodium hydroxide and extracted with chloroform. The organic layer was collected, washed with water, dried over anhydrous sodium sulfate and the solvent was distilled. The residue was crystallized from methanol to give 0.86 g. (98%) of X as colorless rhombs, m.p. 203-205°.

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.48; H, 6.10; N, 16.42.

2,3,3a,4-Tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline (XI).

To a solution of 3.0 g. of sodium in 50 ml. of liquid ammonia was added a suspension of 3.0 g. of VIIa in 50 ml. of toluene and the reaction mixture was stirred at room temperature. After two hours, the ammonia was almost evaporated. Then, the whole was refluxed for 8 hours. Water was added to the mixture and the insoluble solid was collected. Repeated recrystallization from ethanol using decolorizing carbon gave 1.36 g. (54.5%) of XI in yellow needles, m.p. 206-208° dec.; ν max (nujol) cm^{-1}: 1660, 1590; λ (ethanol) mμ (log. ϵ): 267 (4.16); MS (m/e) = 223 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.70; H, 7.02; N, 16.24. Found: C, 76.59; H, 6.79; N, 15.93.

2-Chloro-3-cyanomethylquinoline (XII′).

Perkin and Robinson's procedure was followed exactly; XII′; m.p. 126-127° (isopropyl ether); ν max (nujol) cm^{-1}: 2280 (-CN), 1615 (-N=C-); nmr τ (deuteriochloroform): 6.00 (2H, singlet, $-CH_2CN$), 1.90-2.50 (4H), 1.70 (1H, singlet, C_4-H).

Anal. Calcd. for $C_{11}H_7ClN_2$: C, 65.19; H, 3.48; Cl, 17.49; N, 13.82. Found: C, 65.30; H, 3.64; Cl, 17.57; N, 13.64.

3-Cyanomethylquinoline (XIII′).

Two hundred and fifty mg. of finely powdered XII was mixed with 2.3 ml. of concentrated hydrochloric acid and 0.66 g. of granulated tin was added in small quantities at a time with occasional shaking. After two hours at room temperature, the mixture was made alkaline with aqueous 10% sodium hydroxide in an ice bath because the starting material could not be detected by tlc check. The solution was then taken up in chloroform and after evaporating the solvent, the residue was purified by preparative thin-layer chromatography on silica gel using ethyl acetate-*n*-hexane. From the upper band, 0.017 g. of XIII′ was obtained as colorless, fine needles, m.p. 84-85°; ν max (nujol) cm^{-1}: 2280 (-CN); nmr τ (deuteriochloroform): 6.00 (2H, singlet, $-CH_2CN$), 1.77-2.42 (4H), 1.77 (1H, doublet, J = 2 Hz, C_4-H), 1.14 (1H, doublet, J = 2 Hz, C_2-H); MS (m/e) = 168 (M^+); λ max mμ (ethanol): 230, 234, 283, 305, 310 (sh.), 318.

3-Cyanomethylcarbostyril (XIV′).

This compound had m.p. 234-236° (50% acetic acid): ν max (nujol): 2280 (-CH), 1647 (-NHC=O).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.86; H, 4.45; N, 15.05.

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REFERENCES

(1) T. Tanaka, T. Iwakuma, M. Miyazaki, M. Wagatsuma and I. Iijima, *Chem. Pharm. Bull.* (Tokyo), **20**, 109 (1972).

(2) H. T. Openshaw in "The Alkaloids: Chemistry and Physiology" Vol. VII, R. H. F. Manski, Ed., Academic Press Inc., New York, N.Y., 1960, chapter 12.

(3) J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 4170 (1956).

(4) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and J. Walker, *ibid.*, 1094 (1952).

(5) L. N. Yakhontov, M. Ya. Uritskaya and M. V. Rubtsov, *Zh. Obshch. Khim.*, 34, 1456 (1964).

(6a) B. Witkop, *Experientia*, **10**, 420 (1954); (b) W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, 74, 4516 (1952).

(7) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **103**, 1973 (1913).