Behavior of 2-Pyrazolin-5-ones toward Activated Double Bond Systems: Cyanoethylation of 2-Pyrazolin-5-ones

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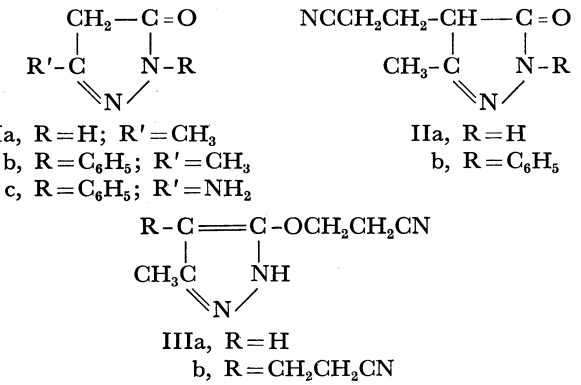
(Received May 21, 1973)

3-Methyl-2-pyrazolin-5-one(Ia) reacts with acrylonitrile to yield either 4,4-di(β-cyanoethyl)-5-hydroxy-3-methylpyrazole(IV) or 1,4,4-tri(β-cyanoethyl)-3-methyl-2-pyrazolin-5-one(V) depending on the amount of reagent and the reaction conditions. Ia reacts with ethyl acrylate or crotononitrile to yield the 4-alkylated derivatives VIII and IX respectively. 3-Methyl-1-phenyl-2-pyrazolin-5-one(Ib) reacts with acrylonitrile to yield only 4,4-di(β-cyanoethyl) derivative XII which on hydrolysis affords the corresponding dicarboxylic acid (XIII). 3-Amino-1-phenyl-2-pyrazolin-5-one(Ic) adds to two molecules of ethyl acrylate or acrylonitrile to yield the 4,4-disubstituted derivatives XIV and XV, but only to one molecule of benzalacetophenone to yield the 4-substituted 3-amino-2-pyrazolin-5-one derivative XVIII. The pyrazolopiperidine derivative(XVI) was obtained on treatment of Ic with ethyl crotonate in the presence of sodium ethoxide.

In continuation of previous works,[1-3] the behavior of the 2-pyrazolin-5-one derivatives (Ia–c) toward a variety of reagents containing activated double bonds was investigated. Kost *et al.*[4] showed that, where as 3-methyl-2-pyrazolin-5-one(Ia) and 4-(β-cyano-ethyl)-3-methyl-2-pyrazolin-5-one(IIa) react with acrylonitrile in *t*-butyl alcohol to yield 5-(β-cyanoethoxy)-3-pyrazole-(IIIa) and 5-(β-cyanoethoxy)-4-(β-cyanoethyl)-3-methylpyrazole(IIIb), respectively, 3-methyl-1-phenyl-2-pyrazolin-5-one(Ib) reacts with the same reagent under the same conditions to yield 4-(β-cyano-ethyl)-3-methyl-1-phenyl-2-pyrazolin-5-one(IIb).



Ia, R=H; R′=CH_3
b, R=C_6H_5; R′=CH_3
c, R=C_6H_5; R′=NH_2

IIa, R=H
b, R=C_6H_5

IIIa, R=H
b, R=CH_2CH_2CN

It has been found that Ia reacts with acrylonitrile in aqueous pyridine to yield either 4,4-di(β-cyano-ethyl)-5-hydroxy-3-methylpyrazole(IV) or 1,4,4-tri(β-cyanoethyl)-3-methyl-2-pyrazolin-5-one(V) depending on the molar ratio of the reactants and the reaction conditions. Thus, when Ia was treated with acrylonitrile in a molar ratio of 1 : 2, compound IV was formed. On the other hand, when Ia was refluxed with excess acrylonitrile in the presence of catalytic amount of potassium hydroxide, tri(β-cyanoethyl)-3-methyl-2-pyrazolin-5-one(V) was formed. Compound V was also formed by the action of acrylonitrile on 1,4-di(β-cyanoethyl)-3-methyl-2-pyrazolin-5-one(VI).

The structure proposed for compound IV was deduced from analytical data, non-identity with the known IIIb and VI, and its preparation by the action of acrylonitrile on IIa. Hydrolysis of IV with acetic acid–hydrochloric acid mixture affords 4,4-di(β-carboxyethyl)-5-hydroxy-3-methylpyrazole (VII). The IR spectrum of IV shows no ring CO absorption but a band extending over 2400—2700 cm^{-1} for the chelated hydroxyl group. Similar spectra were reported for C-4 alkylated 1-unsubstituted-2-pyrazolin-5-ones.[5] The absence of ring CO absorption in the IR spectrum indicates that IV exists mainly, at least in solid state, in the 5-hydroxypyrazole structure.

Attempts to obtain a mono β-cyanoethyl derivative of Ia in pyridine medium were unsuccessful. Even when limited quantities of acrylonitrile were used under conditions[6,7] favorable for monocyanoethylation, the isolable product was compound IV and unchanged Ia. This is similar to the behavior of many compounds containing activated methylene group, where the isolation of a mono β-cyanoethyl derivative is difficult as has been reported.[6-10]

In contrast to the behavior of Ia toward acrylonitrile, we have found that it adds to only one molecule of either of ethyl acrylate or crotononitrile to yield 4-(β-ethoxycarbonylethyl)-5-hydroxy-3-methylpyrazole (VIII) and 4-(β-cyano-α-methylethyl)-5-hydroxy-3-methylpyrazole (IX or possible tautomers), respectively. Compounds VIII and IX were also obtained by the action of hydrazine hydrate on diethyl α-acetylglutamate(X) and ethyl 1-acetyl-3-cyano-2-methylbutyrate(XI), respectively. That acrylonitrile easily effects dialkylation of Ia, whereas ethyl acrylate and crotononitrile effect only mono alkylation under more severe conditions is in accordance with the sequence of reactivity of these reagents as Micheal acceptors.[11] A similar discrepancy in behavior of many

1) M. H. Elnagdi, N. A. L. Kassab, S. M. Fahmy, and F. A. EL-All, *J. Prakt. Chem.*, (in press).
2) M. H. Elnagdi and S. A. Abdalla, *J.Prakt. Chem.*, (in press).
3) M. H. Elnagdi and M. Ohta, This Bulletin, **46**, 1830 (1973).
4) A. N. Kost, S. I. Seminov, R. S. Sagitallin, and V. V. Ershov, *Zh. Obshch. Khim.*, **30**, 2286 (1960).
5) R. Jones, A. J. Ryan, S. Sternhell, and S. E. Wright, *Tetrahedron*, **19**, 1497 (1963).
6) A. D. Campell, *J. Chem. Soc.*, **1954**, 1377.
7) A. D. Campell and I. D. R. Stevens, *ibid.*, **1956**, 959.
8) E. C. Leonard, "Vinyl and Diene Monomers", Part I, J. Wiley & Sons, New York (1970), p. 93.
9) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **64**, 2880 (1942).
10) H. A. Bruson, "Organic Reactions," ed. by R. Adams, J. Wiley and Sons, New York (1949), Vol. V, p. 101.
11) E. D. Bergmann "Organic Reactions" Vol X, ed. by R. Adams, J. Wiley & Sons, New York (1959), Chapter 3, p. 205.

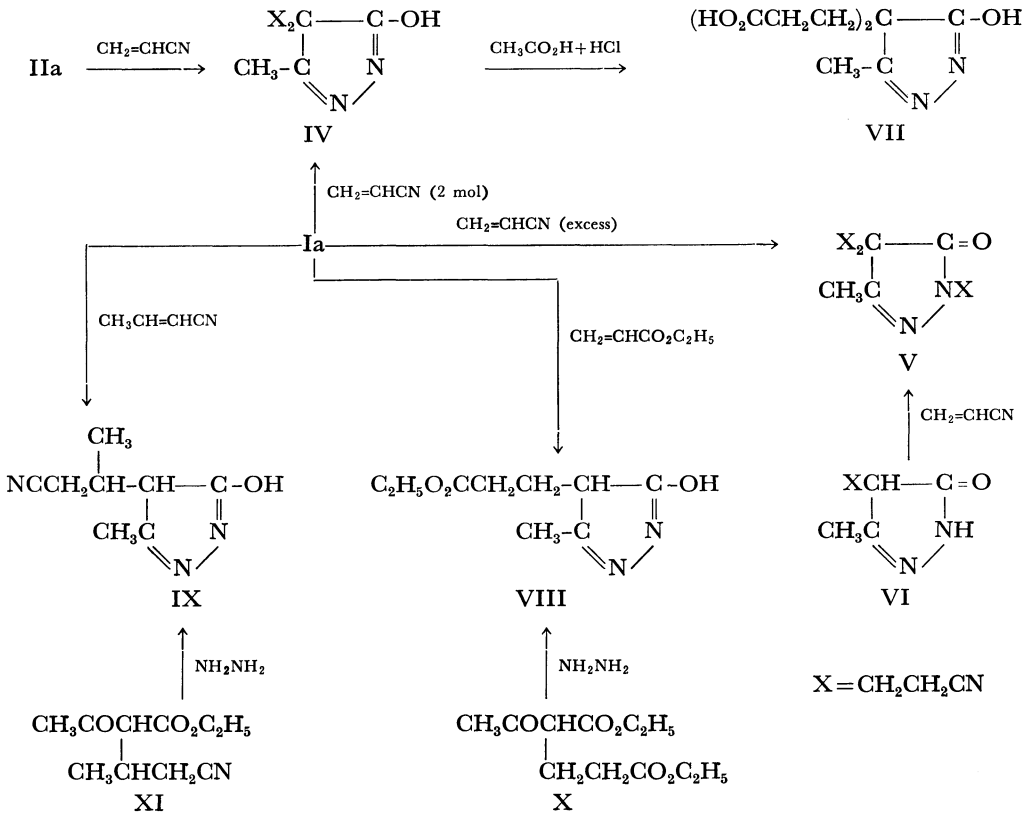
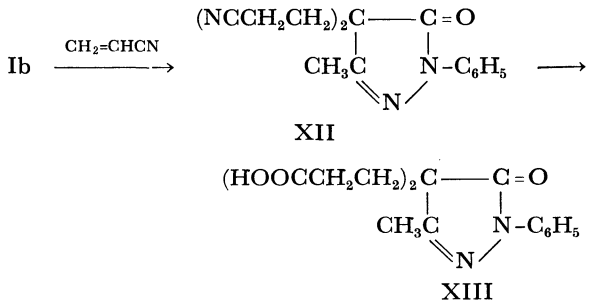


Chart 1

active methylene compounds toward the action of these reagents has been reported.[12-14]

An investigation of the behavior of Ib toward acrylonitrile in aqueous pyridine solution shows that it reacts with two molecules of the reagent yield the 4,4-di(β-cyanoethyl)-1-phenyl-3-methyl-2-pyrazolin-5-one derivative (XII), which on hydrolysis with acetic acid–hydrochloric acid mixture affords the corresponding 4,4-di(β-carboxyethyl) derivative(XIII).



The behavior of 3-amino-1-phenyl-2-pyrazolin-5-one(Ic) toward the action of various reagents containing an activated double bond system was also investigated. Treatment of Ic with ethyl acrylate or acrylonitrile resulted in the formation of products, the analytical data of which indicated that two molecules of either of the reagents had been added and for which structures XIV and XV were proposed. Many isomeric structures for the reaction products of Ic with ethyl acrylate or acrylonitrile are possible. However, the IR spectra of either of the products indicated that the ring CO and the amino group are not involved in the reaction. The 4,4-dialkylated structure (*cf.* XIV and XV) is preferable to the possible 1,4-dialkylated isomer based on analogy to the behavior of Ia, b and the stability of the reaction products toward the action of acetic acid[1,2] and amines.[15] The weak reactivity of possition 2 and the amino group in 3-amino-1-phenyl-2-pyrazolin-5-one has been reported.[1]

We have found that Ic reacts with ethyl crotonate in the presence of sodium ethoxide to yield the pyrazolopiperidine derivative XVI. The structure of XVI was inferred from analytical and spectral data, and its synthesis *via* the action of phenylhydrazine on α-ethoxycarbonyl-β-methylglutamonitrile (XVII). The discrepancy in behavior between Ic and Ia toward the action of ethyl acrylate can be rationalized in terms of increment of reactivity of the methylene group in Ic as compared to that of Ia, induced by the presence of amino group on C-3 which is tautomeric with the imino form.

The compound Ic adds also the benzalacetophenone

12) *cf.* the discrepancy in the behavior of active methylene ketones on treatment with acrylonitrile, ethyl acrylate and crotononitrile, *ibid.*, Tables X—XII.

13) H. A. Bruson and T. W. Riemer, *J. Amer. Chem. Soc.*, **64**, 2850 (1942).

14) H. A. Bruson, *ibid.*, **64**, 2457 (1942).

15) *cf.* dicyanoethylation of *N*-cyanoethylated compounds by the action of amines, P. Buckua, *Zh. Obshch. Khim.*, **34**, 2093 (1964); E. C. Leonard, "Vinyl and diene monomers," Part I Copyright, J. Wiley & Sons, New York (1970), p. 33.

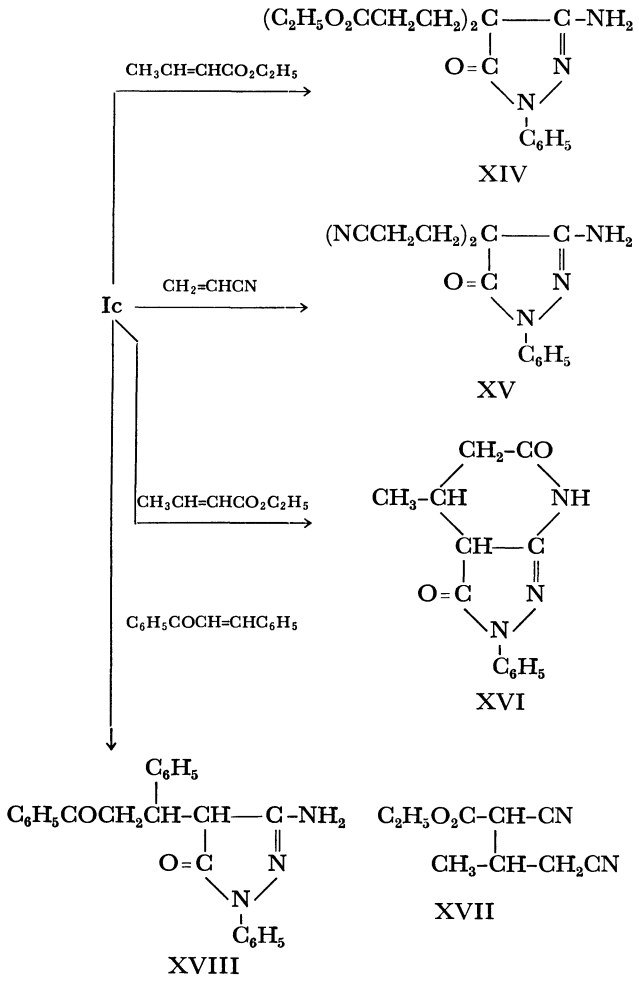


Chart 2

to yield compound XVIII. This is similar to the behavior of Ib toward the same reagent.[16]

Experimental

All melting points were determined on a micro hot stage and are uncorrected. The IR spectra were recorded with a Hitachi Grating IR spectrophotometer Model EPI-G3.

4,4-Di(β-cyanoethyl)-5-hydroxy-3-methylpyrazole (IV). *1) From 3-Methyl-2-pyrazolin-5-one (Ia)*: To a solution of acrylonitrile(10 ml) in pyridine(150 ml) and water(50 ml) was added 10 g of Ia. The reaction mixture was refluxed for 6 hr and the solvent was evaporated *in vacuo* to leave a residue which was purified by crystallization from water to give 15.5 g of IV. Colorless crystals, mp 159 °C. IR: 2920—2600(chelated OH), 2230 cm^{-1} (CN). Found: C, 58.31; H, 5.84; N, 27.80%. Calcd for $C_{10}H_{12}ON_4$: C, 58.88; H, 5.92; N, 27.44%.

2) From 4-(β-Cyanoethyl)-3-methyl-2-pyrazolin-5-one (IIa). To a solution of acrylonitrile(1.6 ml) in pyridine(50 ml) and water (70 ml) was added 3 g of IIa. The reaction mixture was refluxed for 10 hr and then evaporated *in vacuo*. The residue was collected, recrystallized and identified(mp and mixed mp) as IV. Yield, 2.5 g.

1,4,4-Tri(β-cynoethyl)-3-methyl-2-pyrazolin-5-one (V). *1) From Ia.* To a solution of acrylonitrile(1.0 ml) in pyridine(30 ml) and water(10 ml) was added 2.0 g of Ia and then one drop of concentrated potassium hydroxide. The mixture was refluxed for 10 hr and left to stand overnight at room temperature. The solvent was removed *in vacuo* and the resulting oily residue was dissolved in hot ethanol. The crystals, which separated on standing, were recrystallized from ethanol to yield 1.8 g of V, colorless crystals, mp 89 °C. IR: 2220(CN), 1700(ring CO) cm^{-1}. Found: C, 60.44; H, 5.84; N, 27.19%. Calcd for $C_{13}H_{15}ON_5$: C, 60.68; H 5.88; N, 27.22%.

2) From 1,4-Di(β-cyanoethyl)-3-methyl-2-pyrazolin-5-one(VI). Compound VI was treated with acrylonitrile using the same experimental procedure as above and the product was identified (mp and mixed mp) as V. Yield, 51%.

4,4-Di(β-carboxyethyl)-5-hydroxy-3-methylpyrazole (VII). A solution of 3.0 g of IV in acetic acid (30 ml) was mixed with 10 ml of concentrated hydrochloric acid and refluxed for 3 hr. The solvent was removed *in vacuo* and the resulting solid product was crystallized from water to yield 1.5 g of VII, colorless crystals, mp 230 °C (decomp.). Found: C, 49.49; H, 5.94; N, 11.59%. Calcd for $C_{10}H_{14}O_5N_4$: C, 49.58; H, 5.83; N, 11.57%.

4-(β-Ethoxycarbonylethyl)-5-hydroxy-3-methylpyrazole (VIII). *1) From Ia and Ethyl Acrylate*: To a solution of ethyl acrylate (5.0 ml) in ethanol(100 ml) and water(50 ml) was added 5.0 g of Ia. One drop of concentrated potassium hydroxide was then added and the reaction mixture was refluxed for 6 hr. The solvent was then removed *in vacuo* and the oily residue formed was dissolved in benzene and petroleum ether was added. The crystals separated were collected by filtration and recrystallized from benzene to yield 4.7 g of VIII, colorless crystals, mp 100 °C. IR: 2900—2675(OH), 1740 (ester CO)cm^{-1}. Found: C, 54.74; H, 7.06; N, 14.08%. Calcd for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%.

2) From X and Hydrazine Hydrate. To a solution of X (2.0 g) in ethanol(20 ml) was added hydrazine and the mixture was refluxed for 2 hr. The solvent was removed *in vacuo* and the residue was worked up as described above. The product was identified (mp and mixed mp) as VIII. Yield 1.6 g.

4-(β-Cyano-α-methylethyl)-5-hydroxy-3-methylpyrazole (IX). To a solution of crotononitrile(7.0 ml) in pyridine (150 ml) and water (50 ml) was added 10 g of Ia. One drop of potassium hydroxide solution was added and the reaction mixture was refluxed for 24 hr. The solvent was removed *in vacuo* and the residue was dissolved in a small quantity of water and acidified with 10 ml of acetic acid. The solid product separated on being left to stand was collected and crystallized from water to yield 9.0 g of IX, colorless crystals, mp 193 °C. IR: 2900—2650(OH), 2240(CN), 1690(ring CO)cm^{-1}. Found: C, 58.19; H, 6.54; N, 25.30%. Calcd for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44%.

The same compound(IX) was similarly obtained by the reaction of ethyl 1-acetyl-3-cyano-2-methylbutyrate(XI) and hydrazine hydrate.

4,4-Di(β-cyanoethyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (XII). To a solution of acrylonitrile(10 ml) in pyridine(150 ml) and water(50 ml) was added 9.0 g of Ib. The mixture was refluxed for 10 hr, evaporated *in vacuo* and the residual oily product was dissolved in hot ethanol. The crystals separated on cooling were collected and recrystallized from ethanol to give 10 g of XII, mp 74 °C. IR: 2220(CN), 1700(ring CO)cm^{-1}. Found: C, 68.98; H, 5.45; N, 20.01%. Calcd for $C_{16}H_{14}ON_4$: C, 69.05; H, 5.07; N, 20.13%.

4,4-Di(β-carboxyethyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (XIII). Compound XII was treated with acetic acid

16) A. Mustafa, M. Fleifel, M. Ali, and N. M. Hassan, *Ann. Chem.*, **739**, 75 (1970).

and hydrochloric acid by the same procedure as for the preparation of VII. The solid product obtained upon evaporation of the solvent *in vacuo* was crystallized from water to give colorless crystals of XIII, mp 142 °C, in a yield of 80%. Found; C, 60.27; H, 5.70; N, 8.79%. Calcd for $C_{16}H_{18}O_5N_2$: C, 60.37; H, 5.70; N, 8.80%.

3-Amino-4,4-di(β-ethoxycarbonylethyl)-1-phenyl-2-pyrazolin-5-one (XIV). This compound was obtained by a similar procedure to that for XII. Mp, 84 °C, Yield 12.0 g. IR: 1745, 1725(ester CO), 1710(ring CO), 3450, 3355 (NH_2) cm^{-1}. Found: C, 60.43; H, 6.77; N, 12.11%. Calcd for $C_{25}H_{25}O_5N_3$: C, 60.78; H, 6.71; N, 11.19%.

3-Amino-4,4-di(β-cyanoethyl)-1-phenyl-2-pyrazolin-5-one (XV). To a solution of acrylonitrile(5.0 ml) in ethanol(150 ml) and water(50 ml) was added 5.0 g of Ic and the mixture was worked up as for XIV. The solid product obtained on evaporation of the solvent was crystallized from water to give 6.0 g of XV, mp 164 °C. IR: 3390, 3300, 3190(NH_2), 2220(CN), 1710(ring CO) cm^{-1}. Found: C, 64.32; H, 5.40; N, 25.24%. Calcd for $C_{15}H_{15}ON_5$: C, 64.06; H, 5.47; N, 24.90%.

2,3-Dihydro-4-methyl-2-phenylpyrazolo[3,4-b] piperidine-3,6-dione (XVI). *1) From Ic and Ethyl Crotonate*: To a solution of ethyl crotonate(3 ml) in pyridine(150 ml) and water (50 ml) containing one drop of concentrated potassium hydroxide solution was added 7.0 g of Ic. The mixture was refluxed for 10 hr and then evaporated *in vacuo*. The residual oil was treated with sodium ethoxide solution (perpared from 2.0 g of sodium and 150 ml of ethanol) and the mixture was refluxed for 2 hr and again evaporated *in vacuo*. The oil was dissolved in water(100 ml) and acidified with acetic acid. The precipitates were collected by filtration and crystallized from ethanol to give 4 g of XVI, colorless crystals, mp 233 °C. IR: 3130(NH), 1710—1690, 1645—1630(ring CO), 1590(CN) cm^{-1}. Found: C, 63.97; H, 5.33; N, 17.10%. Calcd for $C_{13}H_{13}O_2N_3$: C, 64.18; H, 5.39; N, 17.28%.

2) From Phenylhydrazine and XVII: To a sodium ethoxide solution (prepared from 5.0 g of sodium and 160 ml of ethanol) was added, 12 g of XVII and 7 ml of phenylhydrazine. The mixture was refluxed for 16 hr and then evaporated *in vacuo*. The residue was treated as above and the product was identified (mp and mixed mp) as XVI. Yield, 2.0 g.

3-Amino-4-(1-phenyl-2-benzoylethyl)-1-phenyl-2-pyrazolin-5-one (XVIII). To a sodium ethoxide solution(prepared from 3.0 g of sodium and 150 ml of ethanol) were added, 8.5 g of Ic and 5.0 g of benzalacetophenone. The reaction mixture was refluxed for 6 hr and then evaporated *in vacuo*. The residue was dissolved in water and acidified with concentrated hydrochloric acid. The precipitates were collected by filtration and crystallized from ethanol to yield 6.6 g of XVIII, colorless crystals, mp 300 °C. Found: C, 75.10; H, 6.10; N, 10.58%. Calcd for $C_{24}H_{21}O_2N_3$: C, 75.15; H, 5.52; N, 10.96%.