New Syntheses of Condensed Heterocycles from Isoxazole Derivatives. IV. Benzimidazol-2(3*H*)ones and 1-*H*-1,5-benzodiazepin-2(3*H*)one

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A new synthesis of the title compounds is described. Catalytic hydrogenation of 3-*R*-5-*R'*-2'-nitro-4-isoxazolecarboxanilides (III) yield compounds IV which were cyclized by refluxing in toluene with traces of *p*-toluenesulphonic acid. In contrast to IVa which gave directly 3-acetyl-4-phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (Va), compounds IVb and IVc afforded instead the 1-substituted benzimidazolones VIb and VIc, respectively. The structure of VIa, b, and c, VIIb and VIIc has been elucidated by chemical and spectral means including mass and nmr spectra.

The general approach to the 1,5-benzodiazepine system consists in the condensation of *o*-phenylenediamines with β-ketoesters, β-diketones, β-diesters, β-halogenoketones, *etc.* (1). As an extention of our interest in the syntheses of condensed heterocycles from isoxazole derivatives (2,3), it was of interest to us to investigate a new route to obtain 1,5-benzodiazepinones (V) and benzimidazolones (VI);

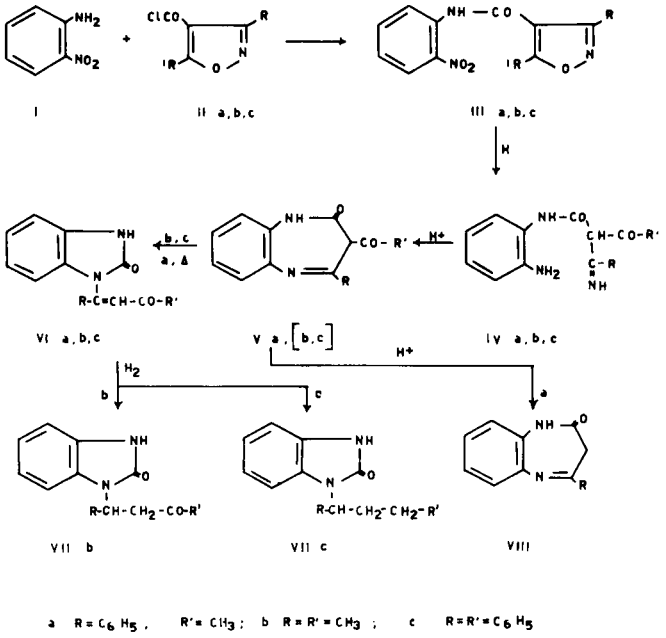
The reaction of *o*-nitroaniline with IIa, b, and c afforded the corresponding 2'-nitro-4-isoxazolecarboxanilides (IIIa, b, and c), suitable intermediates for initial experiments, which were hydrogenated with Raney Nickel to give β-iminodiketones, IV.

Compound IVa, refluxed in toluene with traces of *p*-toluenesulphonic acid and azeotropic water removal, afforded an excellent yield of 3-acetyl-4-phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (Va). Unequivocal evidence for the benzodiazepine structure of Va was given by acid hydrolysis affording the corresponding benzodiazepinone, identical (mixture m.p., ir) with 4-phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (VIII) obtained by independent synthesis (4).

Additional support was the facile ring contraction of Va by fusion giving, like condensed dihydro-1,4-diazepinones (5), the corresponding 1-(4-phenyl-3-buten-2-one-4-yl)benzimidazol-2(3*H*)one (VIa).

Compounds IVb and IVc refluxed in toluene with traces of *p*-toluenesulphonic acid gave instead products VIb and VIc that for their behavior seemed to have a benzimidazole rather than a benzodiazepine structure.

These compounds, indeed, were discovered unchanged after fusion and attempts to bring about the usual ring contraction of benzodiazepinones failed.

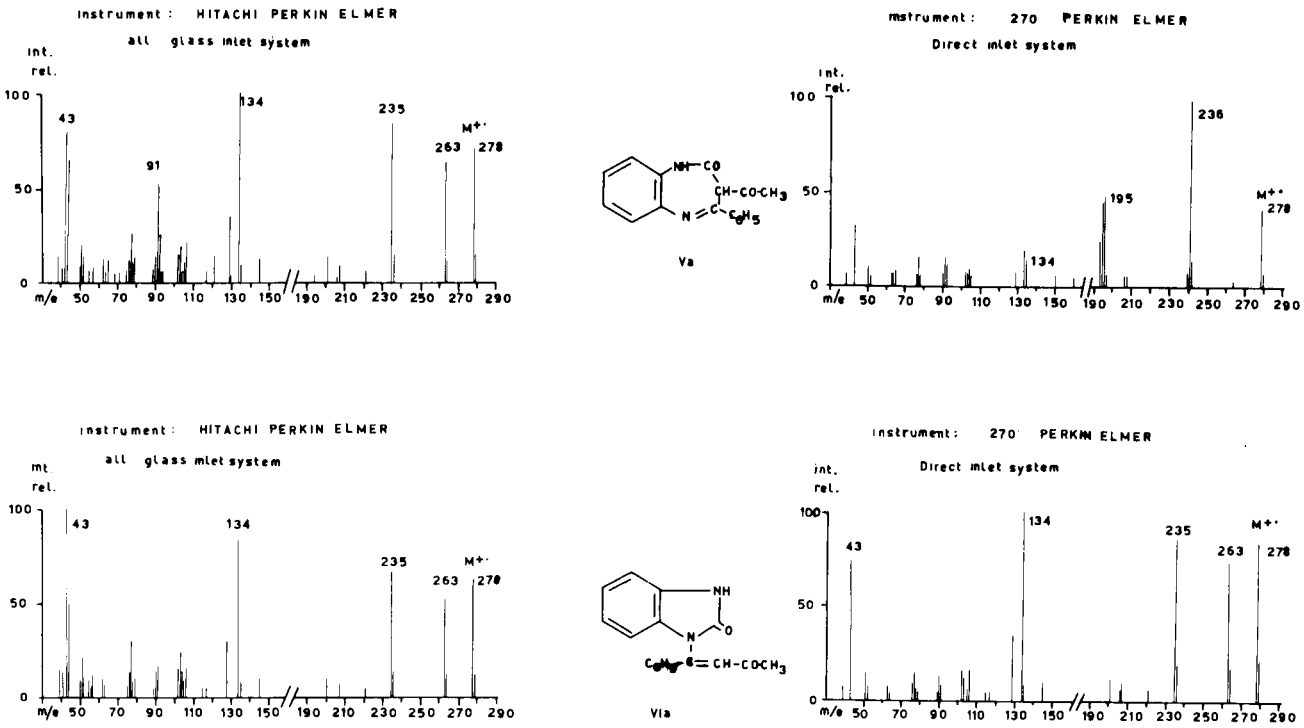


a R = C_6H_5, R' = CH_3; b R = R' = CH_3; c R = R' = C_6H_5

The isolation of VIb and VIc presupposes, evidently, the transitory existence of the corresponding benzodiazepinones (Vb and Vc), but all attempts, including different temperatures and times of condensation, tlc of reaction mixture, failed to yield those products.

On the other hand, nmr spectra of the compounds did not allow us to distinguish unequivocally between the two structures, but definitive evidence in favor of the benzimidazole structure was provided by nmr spectral data of the hydrogenated compounds VIIb and VIIc, respectively.

In fact, the nmr spectrum of VIIb showed signals for the CH_3-CH-CH_2 group (a three protons doublet at δ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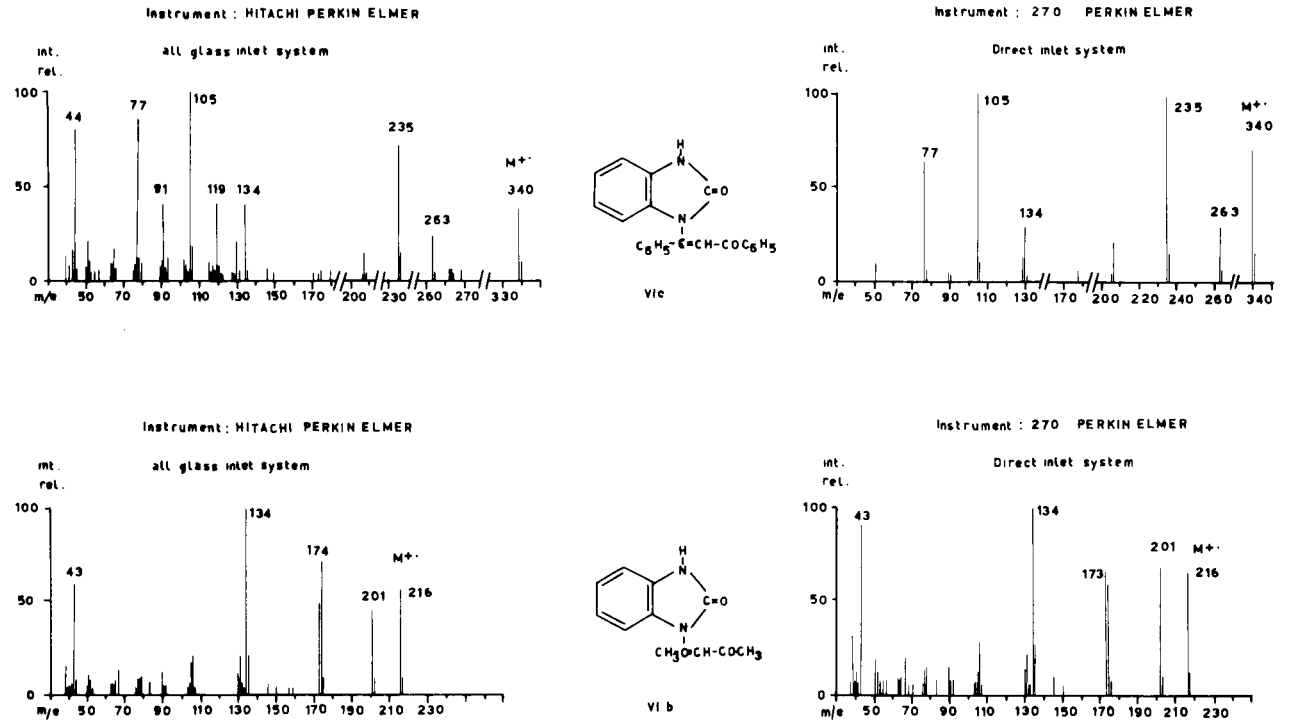
int. rel.
43
91
134
235
263
M+·
278
m/e
Instrument : 270 PERKIN ELMER
Direct inlet system
236
195
134
Va
Instrument : HITACHI PERKIN ELMER
all glass inlet system
Instrument : 270 PERKIN ELMER
Direct inlet system
VIa

Fig.1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all glass inlet system
int. rel.
44
77
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Direct inlet system
VIc
Instrument : HITACHI PERKIN ELMER
all glass inlet system
43
134
174
201
216
Instrument : 270 PERKIN ELMER
Direct inlet system
173
VI b

Fig. 2

1.53, CH_3; a one proton sextet at δ 5.15, CH, and two double doublets at δ 3.10 and 3.44 for CH_2) with relative coupling constants (J_{gem} CH_2 = 17.0 Hz and J_{vic} = 7.0 Hz), and the nmr spectrum of VIIc showed signals for the CH-CH_2-CH_2 group (a four proton multiplet in the region δ 2.6-3.0, CH_2-CH_2, and a one proton multiplet in the region δ 5.6-5.9, CH).

Furthermore, no signals were discovered attributable to a NH amine proton, expected for a tetrahydro benzodiazepine structure. The assigned structure were supported also by mass spectrometry. It was in fact possible to follow the termal ring contraction of Va by means of a low resolution mass spectral examination.

The mass spectrum pattern of Va depends on the inlet system and on the instrument used, and, increasing temperature, becomes very similar to that of benzimidazolone isomer VIa (Fig. 1); must be also noted that the abundance of the ion at m/e 134, probably a benzimidazolone ion structure (6), increase when the spectra were made at more drastic conditions.

In contrast, the mass spectral feature of benzimidazole compounds VIa, b, c are also almost unchanged when the experimental condition are changed; all spectra show a large m/e 134 peak (Fig. 1,2). The unimportant changes observed in this set of spectra are attributable to a partial pyrolysis phenomena.

The low resolution mass spectra investigation of the isomer V and VI types made under several experimental condition, may be a helpful and fast method to distinguish between two structures if our results have general validity.

Most of the compounds described were tested for their action upon the central nervous system and for their analgesic, cardiovascular, antiarthritic, and antinfective properties but no significant activity was observed.

EXPERIMENTAL

An Hitachi Perkin Elmer RMU-6D double focusing and a 270 Perkin Elmer mass spectromers were employed for determination of low resolution 70 e.v. mass spectra. The temperature of ion source was 250°. To follow the dependence of spectra on the temperature, a set of spectra intermediate between those reported in Fig. 1 and 2 was recorded for each compound.

The samples were introduced through the direct inlet system of the 270 P.E. instrument at different temperatures (from heating the probe just to volatize the sample to 250°.

The samples were finally introduced through the all glass inlet system, maintained at 200°, of an Hitachi P.E. instrument.

Nmr spectra were recorded on a Varian 100 MHz and a Jeolco C-60-H spectrometers with TMS as the internal reference. Ir spectra were measured with a Perkin-Elmer Infracord 137 instrument. Microbiological and pharmacological tests were performed by Bristol Laboratories, Syracuse, New York.

Isoxazolecarboxanilides.

A mixture of 0.01 mole of IIa (7), IIb (8), and IIc (7), 0.01 mole of *o*-nitroaniline, 70 ml. of absolute benzene and 1 ml. of dry pyridine was refluxed for 3 hours.

After evaporation of the solvent under reduced pressure, the residue was extracted with ether (3 x 80 ml.). The ether extract was washed with 10% hydrochloric acid, dried (sodium sulfate) and evaporated to afford crude IIIa, b, c, respectively. Two crystallizations were usually sufficient to give material of analytical purity.

2′-Nitro-5-methyl-3-phenyl-4-isoxazolecarboxanilide (IIIa).

Yellow crystals (benzene) m.p. 140° (yield 79%); ir cm^{-1}: 3240 (NH), 1670 (CO).

Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.15; H, 4.05; N, 13.00. Found: C, 62.81; H, 4.11; N, 13.08.

2′-Nitro-3,5-dimethyl-4-isoxazolecarboxanilide (IIIb).

Yellow needles (ethanol) m.p. 125° (yield 82%); ir cm^{-1}: 3360 (NH), 1672 (CO).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.14; H, 4.27; N, 16.07.

2′-Nitro-3,5-diphenyl-4-isoxazolecarboxanilide (IIIc).

White needles (ethanol) m.p. 160° (yield 84%); ir cm^{-1}: 3380 (NH), 1690 (CO).

Anal. Calcd. for $C_{22}H_{15}N_3O_4$: C, 68.56; H, 3.92; N, 10.91. Found: C, 68.34; H, 3.80; N, 10.85.

General Procedure of Hydrogenation.

A mixture of 0.01 mole of the anilide, 100 ml. of ethanol and 2 g. of W-2 Raney Nickel was hydrogenated in a Parr apparatus at 45-50 psi for 8 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the reduced products.

Hydrogenation of IIIa. 2′-Amino-2-benzimidoylacetoacetoanilide (IVa).

Needles (methanol) m.p. 147° (yield 71%); ir cm^{-1}: 3380-3120 (NH_2 and NH), 1650 and 1640 (CO).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.92; H, 5.88; N, 14.16.

1-(3-Penten-2-one-4-yl)benzimidazol-2(3*H*)one (VIb) and Benzimidazol-2(3*H*)one.

A mixture of 0.5 g. of crude hydrogenation product IVb and a trace of *p*-toluenesulfonic acid in 200 ml. of absolute toluene was refluxed for 3 hours with azeotropic removal of water. Upon cooling, the reaction mixture deposited a solid which was recrystallized from ethanol. White scales m.p. 318° (yield 30%). Mixed m.p. with an authentic specimen of benzimidazol-2(3*H*)one (9) was undepressed and ir spectra were identical.

Anal. Calcd. for $C_7H_6N_2O$: N, 20.89. Found: N, 20.89.

The concentration of the toluene solution afforded VIb as an oil which solidified after trituration with a few drops of ethanol, white needles (ethanol) (yield 40%), m.p. 196-197°; uv: λ max, mμ 315 (sh), 280, 224; ir cm^{-1}: 3180 (NH), 1740 and 1700 (CO); nmr (pyridine-d_5): δ2.25 (s, 3H, CH_3); 2.90 (d, 3H, CH_3, J = 0.75 Hz); 6.68 (q, 1H, CH, J = 0.75 Hz); 7.00-7.30 (m, 4H, C_6H_4); 12.60 (broad, 1H, NH); Mass: m/e 216 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.85; H, 5.56; N, 12.56.

Hydrolysis of VIb.

A mixture of VIb (0.3 g.), 20 ml. of ethanol and 1 ml. of

concentrated hydrochloric acid was refluxed for 4 hours, evaporated under reduced pressure and the solid obtained was recrystallized from ethanol. White scales m.p. 317-318° (yield 70%), mixed m.p. with an authentic specimen of benzimidazol-2-(3*H*)one (9) was undepressed and the ir spectra were identical.

Anal. Calcd. for $C_7H_6N_2O$: N, 20.89. Found: N, 20.84.

Hydrogenation of VIb.

1-(Pentan-2-one-4-yl)benzimidazol-2(3*H*)one (VIIb).

Five tenths g. of VIb in 100 ml. of ethanol and 0.1 g. of Pd/C was hydrogenated in a Parr apparatus at 45 psi for 36 hours at room temperature. Removal of the catalyst and evaporation of the ethanol left VIIb as an oil which solidified upon cooling. Crystallization from benzene gave white crystals, m.p. 144-145°; ir cm^{-1}: 3180 (NH); 1720 and 1680 (CO); nmr (pyridine-d_5): δ 1.53 (3H, d, CH_3, J = 7.00 Hz); 2.05 (3H, s, CO-CH_3); 3.10 (1H, dd, CH_2, J = 17.00 Hz, J = 7.00 Hz); 3.44 (1H, dd, CH_2, J = 17.00 Hz, J = 7.00 Hz, 5.16 (1H, sextet CH, J = 7.00 Hz); 7.00-7.40 (4H, m, C_6H_4); 12.04 (1H, broad, NH). Mass: m/e 218 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.23; H, 6.43; N, 12.87.

Hydrogenation of IIIc.

2'-Amino-2-benzimidoyl-2-benzoylacetanilide (IVc).

Light yellow needles (ethanol) m.p. 170° (yield 73%); ir cm^{-1}: 3400-3140 (NH_2 and NH), 1645 and 1635 (CO).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.81; H, 5.40; N, 11.66.

3-Acetyl-4-phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (Va) and benzimidazol-2(3*H*)one.

A mixture of 0.4 g. of IVa and a trace of *p*-toluenesulfonic acid in 180 ml. of absolute toluene was refluxed for 2 hours with azeotropic removal of water. Upon cooling, the reaction mixture deposited a solid which was recrystallized from ethanol, white scales m.p. 317-318° (yield 30%) mixed m.p. with an authentic specimen of benzimidazol-2(3*H*)one (9) was undepressed and the ir spectra were identical.

Anal. Calcd. for $C_7H_6N_2O$: N, 20.89. Found: N, 20.89.

The concentration of the toluene solution afforded Va as white needles m.p. 195-196° (ethanol) (yield 50%); uv: λ max, mμ 340 (sh), 264, 244; ir cm^{-1}: 3190 (NH), 1730 and 1680 cm^{-1} (CO); nmr (pyridine-d_5): δ 1.90 (s, 3H, CH_3); 5.80 (s, 1H, CH); 7.00-8.40 (m, 9H, aromatic); 12.00 (broad, 1H, NH); Mass: m/e 273 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.30; H, 5.04; N, 10.11.

4-Phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (VIII).

A mixture of Va (0.15 g.), 30 ml. of ethanol and 1.5 ml. of hydrochloric acid was refluxed for 30 minutes, evaporated under reduced pressure and the solid obtained was recrystallized from ethanol, white needles m.p. 206° (yield 80%). Mixed m.p. with an authentic specimen of 4-phenyl-1*H*-1,5-benzodiazepin-2(3*H*)one (VIII) (4) was undepressed; the ir spectra were identical; ir cm^{-1}: 3215 (NH), 1700 (CO).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.48; H, 5.16; N, 11.51.

Fusion of Va. 1-(4-Phenyl-3-buten-2-one-4-yl)benzimidazol-2(3*H*)-one (VIa).

Compound Va (0.6 g.) was melted in an oil bath for 10 minutes. Upon cooling a solid product was obtained which was purified by column chromatography on 60 g. of aluminiumoxide (active neutral) and eluted with benzene-ethylacetate (7:3).

Evaporation of eluate yielded a lemon yellow product which melted at 165-166° (methanol); ir cm^{-1}: 3180 (NH); 1700-1680 (CO); nmr (deuteriochloroform): δ 2.25 (3H, s, CO-CH_3); 6.50-7.70 (10H, m, C_6H_4, C_6H_5, and CH); 10.05 (broad, 1H, NH); Mass: m/e 278 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.49; H, 5.05; N, 9.95.

1-(1,3-Diphenyl-2-propen-1-one-3-yl)benzimidazol-2(3*H*)one (VIc).

This compound was obtained from IVc according to the procedure described for Va and Vb. Powder from ethanol m.p. 230-231° (yield 60%); uv: λ max mμ 280 (sh), 274, 266, 242; ir cm^{-1}: 3200 (NH); 1720 and 1680 (CO); nmr (pyridine-d_5): δ 6.60-8.00 (15H, a set of signals for C_6H_4, 2 x C_6H_5 and CH); 12.70 (s, 1H, NH); Mass m/e 340 (M^+).

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 78.07; H, 4.78; N, 7.90.

Hydrogenation of VIc. 1-(1,3-Diphenylprop-1-yl)benzimidazol-2(3*H*)one (VIIc).

A mixture of VIc (0.3 g.), 100 ml. of ethanol and 0.1 g. of Pd/C was hydrogenated in a Parr apparatus at 45 psi for 21 hours at room temperature. Removal of the catalyst and evaporation of the ethanol left a residue (0.25 g.) which was purified by column chromatography on 60 g. of silica gel (Kieselgel 0.05-0.2 mm) and eluted with benzene-ethylacetate (8:2). Evaporation of eluate yielded a white product which melted at 170-171° (benzene); ir cm^{-1}: 3180 (NH); 1700 (CO); nmr (deuteriochloroform): δ 2.60-3.00 (4H, m, CH_2-CH_2); 5.60-5.90 (1H, m, CH); 6.70-7.60 (14H, m, C_6H_4, 2 x C_6H_5); 10.35 (1H, s, NH); Mass: m/e 328 (M^+).

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.59; H, 6.34; N, 8.56.

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REFERENCES

(1) A. R. Katritzky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 8, Academic Press, New York, 1967, p. 66.

(2) E. Ajello, *J. Heterocyclic Chem.*, **8**, 1035 (1971).

(3) E. Ajello, O. Migliara, and V. Sprio, *ibid.*, **9**, 1119 (1972).

(4) W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 828 (1957).

(5) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron Letters*, 4811 (1968).

(6) S. Linke, J. Kurz, and C. Wunsche, *Ann. Chem.*, 936 (1973).

(7) A. Quilico and R. Fusco, *Gazz. Chim. Ital.*, **67**, 595 (1937).

(8) F. P. Doyle and J. H. C. Nayler, *Chem. Abstr.*, **56**:P 5972g (1962).

(9) O. Kym, *J. Prackt. Chem.* (2), 75, 323 (1907).