Naphtho[1′,2′:5,6]pyrano[2,3-*b*][1,5]benzodiazepine Derivatives

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The reaction of 3-(dimethylamino)-1-oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbaldehyde (Ia) with *o*-phenylenediamines or *N*-monosubstituted *o*-phenylenediamines in refluxing glacial acetic acid afforded the corresponding naphtho[1′,2′:5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)ones V in very good yields. A similar result was achieved when the reaction was carried out in refluxing pyridine, using *N*-monosubstituted *o*-phenylenediamine hydrochlorides. The isolation of a significant intermediate as well as the synthesis through a different univocal pathway confirmed the structure of the compounds V.

Moreover the reaction of Ia with *N*-monosubstituted *o*-phenylenediamines in refluxing pyridine generally afforded only low yields of compounds V, sometimes together with naphtho[1′,2′:5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(13*H*)ones VII, isomers of V.

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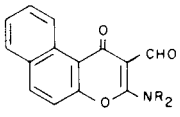
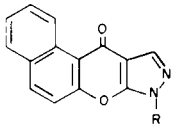
We have previously pointed out that 3-(dialkylamino)-1-oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbaldehydes I are very helpful starting materials to achieve the formation of new heterocyclic rings condensed with the γ-pyrone moiety by reaction with proper reagents provided with two nucleophilic positions (1-3).

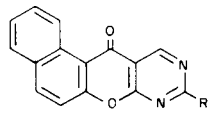
Indeed naphtho[1′,2′:5,6]pyrano[2,3-*c*]pyrazole and 12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine derivatives II (1,3) and III (2,3) were obtained by treating 3-(dimethylamino)-1-oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbaldehyde (Ia) with hydrazines and guanidine, amidines, *etc.*, respectively: the formation of intermediate imino derivatives and their cyclization by intramolecular nucleophilic attack on the 3 position and elimination of dimethylamine were the steps of the reaction.



I



II



III

Ia, R = CH_3
Ib, R = C_2H_5

As a further part of our interest in this chemistry we have now studied the behaviour of Ia in the reaction with suitable 1,2-diamines, in order to achieve the condensation of a diazepine ring with the 1*H*-naphtho[2,1-*b*]pyran system.

The experimental results allowed us to determine the proper conditions to prepare the desired products V in the best yields and to point out that under different conditions, isomers of V may sometimes be obtained.

Actually the treatment of Ia with *o*-phenylenediamines or *N*-monosubstituted *o*-phenylenediamines in refluxing glacial acetic acid led to the formation of naphtho[1′,2′:5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)ones V in very good yields. The suggested addition-elimination mechanism is in accordance with the results recently reported in the literature for a similar case (4) (Scheme 1).

In this connection the reaction of 3-(diethylamino)-1-oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbaldehyde (Ib) and *N*-phenyl-*o*-phenylenediamine in the same above reported conditions afforded a lower yield of Vd, confirming the importance of the steric hindrance of the 3-dialkylamino substituent in the cyclization (1).

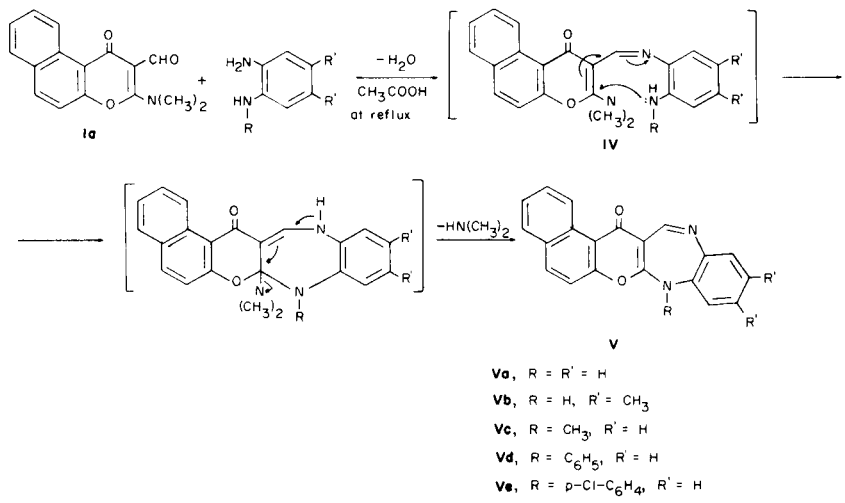
In accordance with the first step of the above reaction pattern, when the reaction of Ia with *N*-phenyl-*o*-phenylenediamine was carried out in glacial acetic acid at room temperature, the intermediate IVd and the benzimidazolyl derivative VIa were isolated, a different cyclization of IVd occuring at a lower temperature. The transformation of IVd into VIa, which takes place through a dehydrogenation step, may most likely start in the reaction solution and go on during the handling with solvents of the reaction crude product (Scheme 2).

On the other hand, when the reaction of Ia with *N*-monosubstituted *o*-phenylenediamines was performed in refluxing pyridine, in the case of *N*-methyl-*o*-phenylenediamine, only Vc was recovered in a low yield, whereas using *N*-phenyl or *N*-(*p*-chlorophenyl)-*o*-phenylenediamine compounds VIa and VIIa or Ve and VIIb, respectively, were obtained (Scheme 3).

The formation of compounds VII, isomers of V, may be explained through the preliminary nucleophilic attack of NH_2 on the 3 position of Ia, followed by elimination of dimethylamine.The subsequent cyclization of the intermediate occurred by nucleophilic addition of NHR to the formyl group, followed by dehydration of the adduct to give the more conjugated and stable VII (Scheme 4).

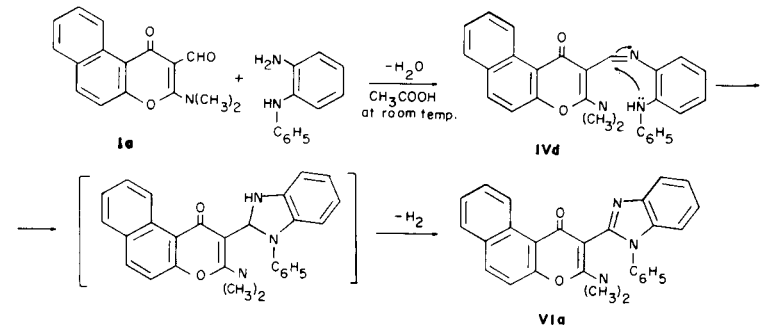
Finally, when Ia reacted with *N*-methyl or *N*-phenyl-*o*-phenylenediamine hydrochloride in refluxing pyridine, only Vc or Vd were obtained in good yields. It is notewor-

Scheme 1

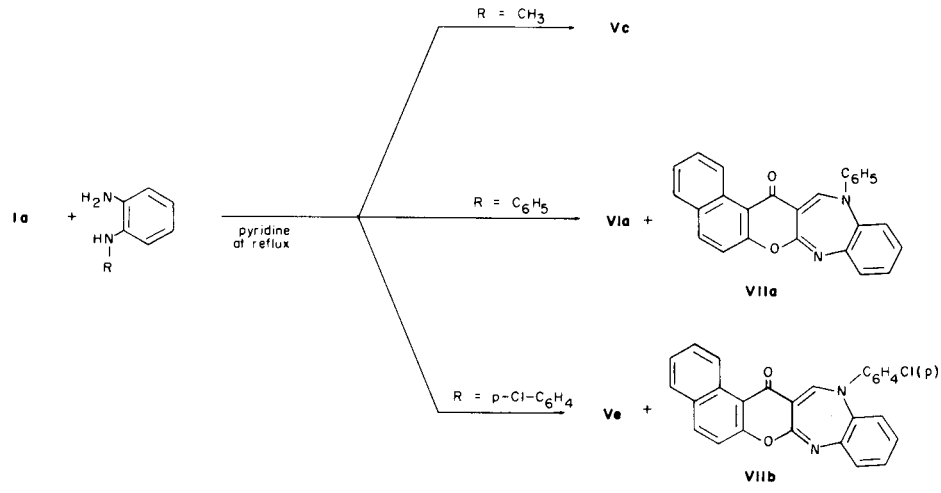


Va, R = R' = H
Vb, R = H, R' = CH_3
Vc, R = CH_3, R' = H
Vd, R = C_6H_5, R' = H
Ve, R = p-Cl-C_6H_4, R' = H

Scheme 2



Scheme 3

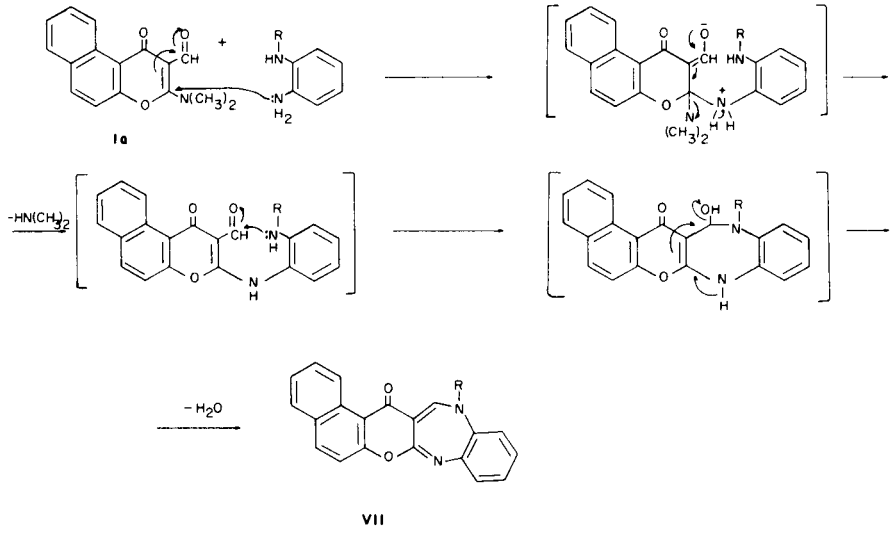


thy that the same result was achieved when the free amines in refluxing acetic acid were used.

All of the above results afforded evidence of the importance of sufficiently high proton concentration in achieving the unequivocal formation of compounds V.

The structures attributed to the compounds described in the present paper completely agree with the results of elemental analyses and with ir, pmr, and mass spectral

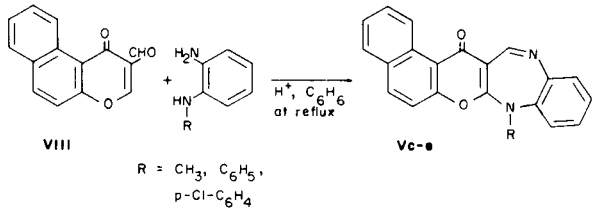
Scheme 4



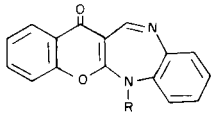
data (see Experimental).

It is interesting to observe that the formation of compounds V was also achieved by reaction of 1-oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbaldehyde (VIII) with *N*-monosubstituted *o*-phenylenediamines in refluxing benzene in the presence of *p*-toluenesulfonic acid (Scheme 5). This result provides a further evidence of the structures attributed to the isomeric compounds V and VII.

Scheme 5



Indeed it has been reported recently (4) that 4-oxo-4*H*-[1]benzopyran-3-carbaldehyde reacted under the same conditions with *N*-monosubstituted *o*-phenylenediamine to give only benzopyranobenzodiazepinones IX.



IX

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 257 spectrophotometer (in potassium bromide pellets). Pmr spectra were recorded on a Perkin-Elmer R12 spectrometer (60 MHz), using tetramethylsilane as an internal reference (τ = 10). Mass spectra were taken on a Varian CH7 mass spectrometer (70 eV). Elemental analyses were performed by Laboratorio di Microanalisi, Istituto Carlo Erba per Ricerche Terapeutiche, Milan.

Naphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)ones (V).

Method A.

A mixture of 3.6 mmoles (0.96 g) of Ia (1), 3.6 mmoles of the suitable *o*-phenylenediamine and 20 ml of glacial acetic acid was heated at reflux for 1 hour. By allowing the resulting solution to stand overnight at room temperature, the nearly pure solid compound V was separated out. Compound V was filtered, washed with water, dried and crystallized from benzene.

In the case of Vc the reaction solution was cooled, diluted with water and made alkaline by the addition of sodium carbonate. After stirring for 30 minutes at room temperature, the resulting precipitate was collected, washed with water and crystallized from acetone to obtain pure Vc.

By the above procedure the following compounds V were prepared:

Naphtho(1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)one (Va).

Starting from 0.39 g of *o*-phenylenediamine, 1.05 g (93.8% yield) of Va was obtained. After crystallization the compound was a white solid which melted at 266-267°; ir: 3330 (NH), 1648 cm^{-1} (CO); pmr (deuteriotrifluoroacetic acid): τ2.47-1.57 (m, 9H, H-2, 3, 4, 5, 6, 9, 10, 11, 12), 0.63 (s, 1H, H-14), 0.36 (mc, 1H, H-1); ms: m/e 312 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 76.92; H, 3.92; N, 9.00.

10,11-Dimethylnaphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)one (Vb).

1.02 g of compound Vb (82.9% yield) was obtained from 0.49 g of 4,5-dimethyl-*o*-phenylenediamine. Crystallization resulted in a yellow solid with mp 272-273°; ir: 3340 (NH), 1647 cm^{-1} (CO); pmr (deuteriotrifloroacetic acid): τ 7.54 (s, 6H, CH_3), 2.55-1.69 (m, 7H, H-2, 3, 4, 5, 6, 9, 12), 0.78 (s, 1H, H-14), 0.49 (mc, 1H, H-1); ms: 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, 77.35; H, 4.74; N, 8.05.

8-Methylnaphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)one (Vc).

Compound Vc (0.77 g, 65.8% yield) was obtained from 0.44 g of freshly distilled *N*-methyl-*o*-phenylenediamine. Recrystallizing compound Vc in benzene resulted in white crystals with a mp 279-280°; ir:

1644 cm^{-1} (CO); pmr (deuteriotrifluoroacetic acid): τ 5.78 (s, 3H, CH_3), 2.34-1.45 (m, 9H, H-2, 3, 4, 5, 6, 9, 10, 11, 12), 1.02 (s, 1H, H-14), 0.20 (mc, 1H, H-1); ms: m/e 326 (M^+).

Anal. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.28; H, 4.32; N, 8.58. Found: C, 77.02; H, 4.24; N, 8.41.

8-Phenylnaphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)one (Vd).

Compound Vd (0.81 g, 57.9% yield) was obtained from 0.66 g of *N*-phenyl-*o*-phenylenediamine. Crystallization resulted in a white solid with mp 235°; ir: 1652 cm^{-1} (CO); pmr (deuteriochloroform): τ 2.81-1.86 (m, 14H, H-2, 3, 4, 5, 6, 9, 10, 11, 12 + phenyl H's), 1.61 (s, 1H, H-14), 0.40 (mc, 1H, H-1); ms: m/e 388 (M^+).

Anal. Calcd. for $C_{26}H_{16}N_2O_2$: C, 80.40; H. 4.15; N, 7.21. Found: C, 80.50; H, 4.15; N, 7.12.

8-(4-Chlorophenyl)naphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(8*H*)one (Ve).

Compound Ve (0.68 g, 44.7% yield) was obtained from 0.79 g of *N*-(*p*-chlorophenyl)-*o*-phenylenediamine. Crystallization resulted in a white solid with mp 293-294°; ir 1650 cm^{-1} (CO); pmr (deuteriotrifluoroacetic acid): τ 2.53-1.39 (m, 13H, H-2, 3, 4, 5, 6, 9, 10, 11, 12 + *p*-chlorophenyl H's), 1.45 (s, 1H, H-14), 0.22 (mc, 1H, H-1); ms: m/e 422 (M^+).

Anal. Calcd. for $C_{26}H_{15}ClN_2O_2$: C, 73.85; H, 3.58; N, 6.63; Cl, 8.39. Found: C, 73.94; H, 3.58; N, 6.53; Cl, 8.23.

Method B.

Compound Vc

A mixture of 0.96 g (3.6 mmoles) of Ia, 0.57 g (3.6 mmoles) of *N*-methyl-*o*-phenylenediamine monohydrochloride and 20 ml of pyridine was heated at reflux for 2 hours. After cooling, a whitish crystalline material separated from the dark solution; the solid was then recovered by filtration and washed with ethyl ether, obtaining 0.72 g (61.5% yield) of nearly pure Vc.

Compound Vd.

A mixture of 0.96 g (3.6 mmoles) of Ia, 0.79 g (3.6 mmoles) of *N*-phenyl-o-phenylenediamine monohydrochloride and 20 ml of pyridine was refluxed for 1 hour. The resulting reddish solution was cooled, diluted with water, and made definitively alkaline by the addition of sodium carbonate. After stirring for 30 minutes at room temperature, the yellowish amorphous solid which precipitated was collected by filtration, washed with water and crystallized from acetone, affording 0.69 g (49.3% yield) of Vd.

Method C.

A mixture of 10.0 mmoles (2.24 g) of VIII (5), 10.0 mmoles of the suitable *N*-monosubstituted-*o*-phenylenediamine, 0.2 g of *p*-toluenesulfonic acid and 150 ml of dry benzene was heated at reflux for 3 hours using a Dean-Stark water trap. Continuing in each case as below described the following compounds V were prepared.

Compound Vc.

Freshly distilled *N*-methyl-*o*-phenylenediamine (1.22 g) was used in the reaction. After collecting by filtration the whitish solid present in the hot reaction mixture, the filtrate was concentrated to about 80 ml and allowed to stand at room temperature, giving 0.99 g of pure crystalline Vc.

The column chromatography (silica gel/chloroform-acetone, 1:1) of the previously sepatated whitish solid afforded 0.08 g of additional product (total yield 32.8%).

Compound Vd

N-Phenyl-*o*-phenylenediamine (1.84 g) was used. After cooling, the benzene reaction solution was washed with water, dried (sodium sulfate) and evaporated under reduced pressure. By adding a little acetone to the oil residue the separation of nearly pure crystalline Vd (1.19 g) was obtained.

By concentrating the mother liquor to a low volume, an additional crop (0.19 g) of the compound was recovered (total yield 35.6%).

Compound Ve.

N-(*p*-Chlorophenyl)-*o*-phenylenediamine (2.19 g) was used. The benzene reaction solution was cooled, washed with water, dried (sodium sulfate) and evaporated under reduced pressure. By adding a little acetone to the resulting mixture of whitish solid and dark oil, 1.65 g (39.0% yield) of crystalline Ve was obtained.

Compounds IVd and VIa.

A mixture of 0.24 g (0.9 mmoles) of Ia, 0.17 g (0.9 mmoles) of *N*-phenyl-*o*-phenylenediamine and 5 ml of glacial acetic acid was stirred at room temperature for 20 minutes. The resulting yellow solution was then poured onto crushed ice and water, made alkaline with sodium carbonate, and again stirred at room temperature for 30 minutes. The yellow amorphous solid which precipitated was collected by filtration, washed with water and suspended in a little acetone. The mixture was allowed to stand at room temperature until orange needles of nearly pure IVd separated out, which were recovered (0.12 g, 30.8% yield) and recrystallized from acetone (mp 170-172°) (caution must be used because further recrystallizations make the quality of the product worse); ir: 3265 (NH), 1630 (CO), 1574 cm^{-1} (γ-pyrone C=C); pmr (deuteriochloroform): τ 6.86 (s, 6H, CH_3), 3.18-1.88 (m, 15H, H-5, 6, 7, 8, 9 + phenyl H's + phenylene H's + NH), 0.75 (s, 1H, CH=N), -0.15 (mc, 1H, H-10); ms: m/e 433 (M^+).

Anal. Calcd. for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.40; H, 5.27; N, 9.56.

The acetone mother liquor was then allowed to concentrate at room temperature for a long period of time. Crystalline nearly pure VIa separated out, and recrystallized from benzene yielding 0.11 g (28.2%) of white crystals melting at 289-290°; ir: 1626 (CO), 1560 cm^{-1} (γ-pyrone C=C); pmr (deuteriotrifluoroacetic acid): τ 7.00 (s, 6H, CH_3), 2.73-1.60 (m, 14H, H-5, 6, 7, 8, 9 + 1'-phenylbenzimidazol-2'-yl H's), 0.34 (mc, 1H, H-10); ms: m/e 431 (M^+).

Anal. Calcd. for $C_{28}H_{21}N_3O_2$: C, 77.94; H, 4.91; N, 9.74. Found: C, 77.85; H, 5.04; N, 9.62.

The Reaction of Ia with *N*-Monosubstituted *o*-phenylenediamines in Refluxing pyridine.

A mixture of 0.96 g (3.6 mmoles) of Ia, 3.6 mmoles of the suitable *N*-monosubstituted *o*-phenylenediamine and 20 ml of pyridine was refluxed for 8 hours, and the resulting reddish solution was then treated in each case as described below.

Compound Vc.

Freshly distilled *N*-methyl-*o*-phenylenediamine (0.44 g) was used in the reaction. After cooling, the reaction solution was poured onto crushed ice and water and stirred at room temperature for 30 minutes. The amorphous solid which precipitated was collected by filtration, washed with water, dried and crystallized from benzene with charcoal, giving 0.23 g (19.7% yield) of pure Vc.

Compounds VIIa and VIa.

N-Phenyl-*o*-phenylenediamine (0.66 g) was used. After the reaction solution was allowed to stand overnight at room temperature, the yellow crystalline solid which separated was collected by filtration. It consisted of pure 13-phenylnaphtho[1',2':5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(13*H*)one (VIIa) (0.25 g) that melted at 279° after recrystallization from acetone; ir: 1657 cm^{-1} (CO); pmr (deuteriotrifluoroacetic acid): τ2.60-1.57 (m, 14H, H-2, 3, 4, 5, 6, 9, 10, 11, 12 + phenyl H's), 0.44 (mc, 1H, H-1), 0.43 (s, 1H, H-14); ms: m/e 388 (M^+).

Anal. Calcd. for $C_{26}H_{16}N_2O_2$: C, 80.40; H, 4.15; N, 7.21. Found: C, 80.23; H, 4.11; N, 7.10.

The pyridine filtrate was then diluted with ice-water and the amorphous solid which precipitated was collected and washed with water.

After adding acetone to this crude product and stirring the mixture, the insoluble material was recovered and crystallized from benzene, affording an additional crop (0.05 g) of pure VIIa (total yield 21.4%).

The acetone solution was then allowed to evaporate at room temperature until a dark solid separated out, which afforded 0.11 g (7.1% yield) of white crystalline VIa, after several recrystallizations from chloroform.

Compound VIIb and Ve.

N-(*p*-Chlorophenyl)-*o*-phenylenediamine (0.79 g) was used. By allowing the reaction solution to stand overnight at room temperature, the separation of crude 13-(4-chlorophenyl)naphtho[1′,2′:5,6]pyrano[2,3-*b*][1,5]benzodiazepin-15-(13*H*)one (VIIb) was achieved. It was collected by filtration and crystallized from benzene, giving 0.13 g (8.6% yield) of pure orange needles melting at 280-281°; ir: 1657 cm^{-1} (CO); pmr(deuteriotrifluoroacetic acid): τ 2.85-1.44 (m, 13H, H-2, 3, 4, 5, 6, 9, 10, 11, 12 + *p*-chlorophenyl H's), 0.24 (mc, 1H, H-1), 0.07 (s, 1H, H-14); ms: m/e 422 (M^+).

Anal. Calcd. for $C_{26}H_{15}ClN_2O_2$: C, 73.85; H, 3.58; N, 6.63; Cl, 8.39. Found: C, 73.87; H, 3.56; N, 6.64; Cl, 8.42.

By diluting the pyridine filtrate with ice-water the precipitation of a yellowish amorphous solid was achieved. It was then collected, washed with water and crystallized form acetone, affording 0.13 g of nearly pure Ve (8.6% yield).

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