About the Synthesis of [1,2]Diazepinoindole Derivatives from Ethyl 2-(1-Methylindole)acetate, 2-Indole and 3-Indoleacetohydrazones.

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The Vilsmeier-Haack reaction with ethyl 2-(1-methylindole)acetate and *N,N*-Dimethylamides/phosphorus oxychloride gave (65-85%) of ethyl 2-(3-acyl-1-methylindole)acetates **2**, which when boiled with hydrazine yielded about 90% of 4,5-dihydro-6-methyl-4-oxo-3*H*[1,2]diazepino[5,6-*b*]indoles **3**. The attempted cyclization of 2-(1-methylindole)acetohydrazones **6** with acyl (acetyl and benzoyl) chlorides/triethylamine, to [1,2]diazepino[5,6-*b*]indole derivatives was fruitless and the bis(acyl)hydrazones **9** were obtained. Several transformations of **9** are reported. Similarly, the attempted cyclization of 3-indoleacetohydrazones **14** with acetyl chloride/triethylamine to [1,2]diazepino[4,5-*b*]indole derivatives was also fruitless and the bis(acyl)hydrazones **16** were again obtained.

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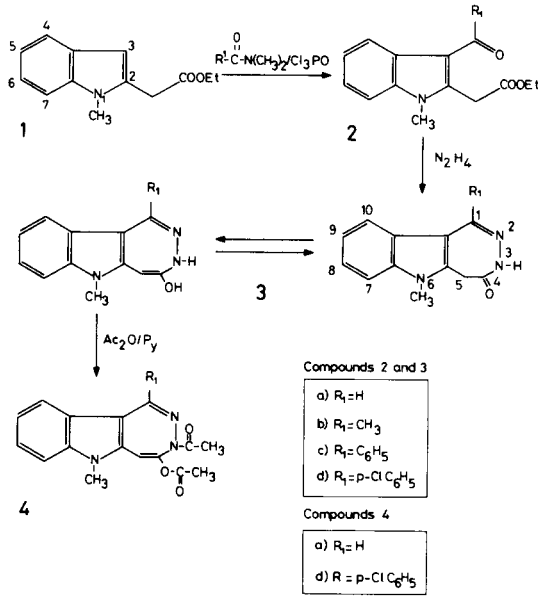
The benzodiazepines are a broad group of psychopharmacologic agents with particular interest for the treatment of anxiety and sleeping disorders [1]. Furthermore a number of diazepines fused with different heterocyclic systems have also been synthesized and studied for their potential psychopharmacologic properties [2]. However, to our knowledge, only three papers have been published on [1,2]diazepinoindoles [2,3,4], with reference to 1*H*[1,2]diazepino[4,5-*b*]indoles [2,3], 3*H*[1,2]diazepino[5,6-*b*]indoles [2] and [1,2]diazepino[6,5,4-*cd*]indoles [4].

This paper is a continuation of our previous report [2] on [1,2]diazepino[5,6-*b*]indoles and [1,2]diazepino[4,5-*b*]-indoles. We describe here an unambiguous and efficient synthesis of 3*H*[1,2]diazepino[5,6-*b*]indoles (Scheme 1) and the results of our fruitless attempted cyclizations of 2-(1-methylindole)acetohydrazones (Scheme 2) and 3-indoleacetohydrazones (Scheme 3) to [1,2]diazepino[5,6-*b*]-indoles and [1,2]diazepino[4,5-*b*]indoles, respectively.

Scheme 1

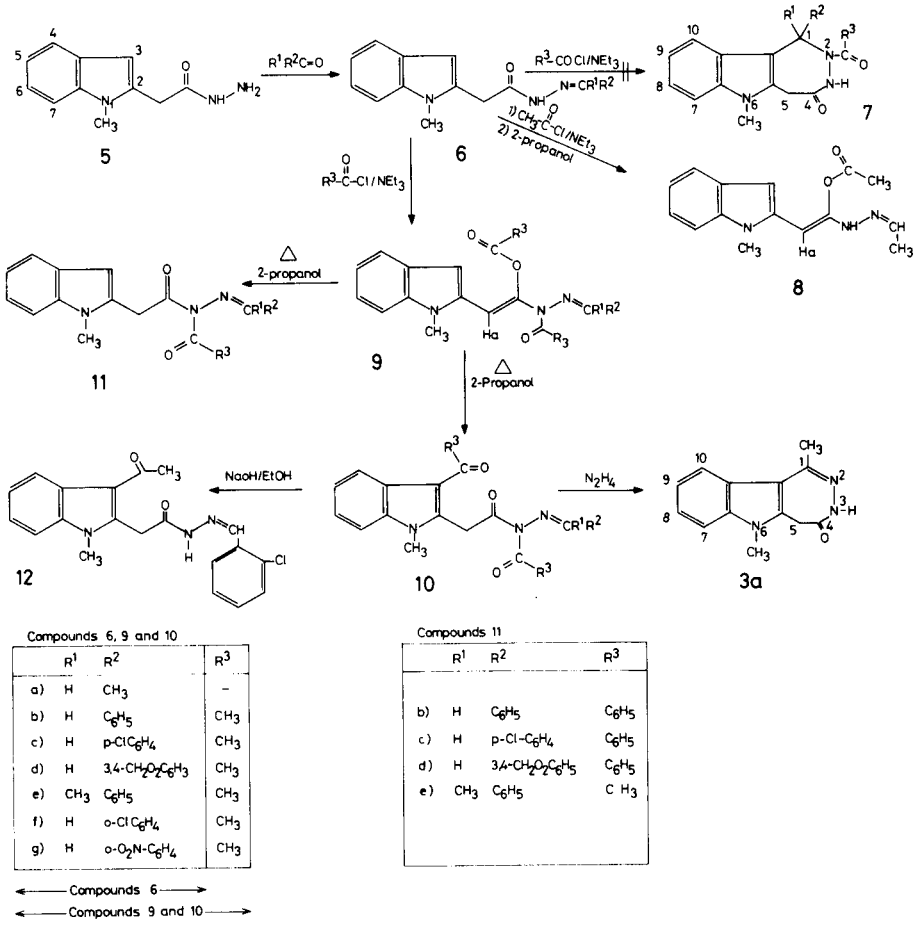


Compound **1** (Scheme 1) obtained by a reported method [2], reacts satisfactorily with different *N,N*-dimethylamides and phosphoryl chloride, according to the Vilsmeier-Haack reaction [5], to give compounds **2** (65-85%). These compounds were characterized by elemental analysis, ir and ^{1}H-nmr spectra which are detailed under the experimental. Upon boiling an ethanol solution of **2** with hydrazine, compounds **3** were obtained (85-95%). The ir spectra (potassium bromide tablets) of **3** showed characteristic bands at about 1650-1660 cm^{-1} (s) and 1600-1610 cm^{-1} (s), assigned to the groups C=O and C=N, respectively, and so the -CONH structural form seems the most representative in the solid state. However, in solution (DMSO-d_6, deuteriochloroform) the ^{1}H-nmr spectra of compounds **3** show signals at about δ = 5.95-6.25 (s, 1H) and 4.30-6.20 (s or broad signal, 1H), which have been assigned to the protons H-5 and -OH, respectively, of the enolic structural form.

When compounds **3a** and **3d** were treated with acetic anhydride/pyridine, the respective compounds **4a** (95%) and **4b** (93%) were obtained, and a signal in the ^{1}H-nmr spectra at about δ = 6.20 (deuteriochloroform, s, 1H) for **4a** and δ = 6.75 (deuteriochloroform/trifluoroacetic acid, s, 1H) for **4d**, were unambiguously assigned to proton H-5.

In previous papers [6,7] we have reported the cyclization of 2-indolecarbohydrazones [6] and 3-indolecarbohydrazones [6,7] to derivatives of pyridazino[4,5-*b*]indole on treatment with acyl halides/triethylamine. On these bases, the possible similar cyclization of 2-(1-methylindole)acetohydr-

Scheme 2

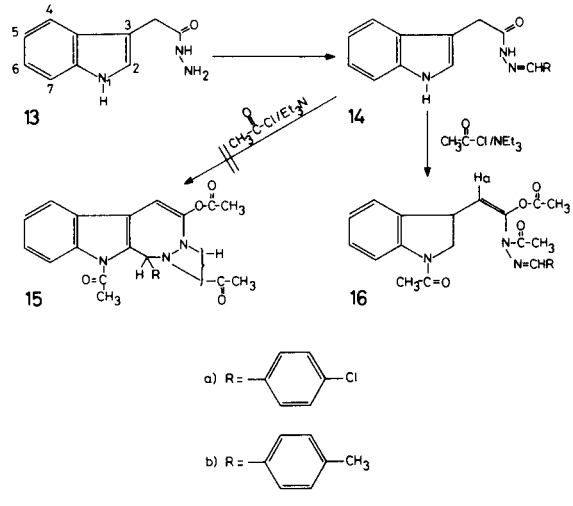


azones **5** (Scheme 2) and 3-indoleacetohydrazones **14** (Scheme 3) to [1,2]diazepinoindole derivatives were now attempted.

The new hydrazones **6** were obtained (90-97%) by standard procedures from the previously reported compound **5** [2] and characterized by elemental analysis and spectral (ir, ^{1}H-nmr) data, which are detailed in the experimental. Their ir spectra show one band at about 3180-3200 cm^{-1} (s) for the NH group and one or two bands in the region 1650-1675 cm^{-1} (s) for the groups C=O and C=N. Their ^{1}H-nmr spectra showed that in all the reported examples the products were mixtures of two isomers because of the protons or groups of equivalent protons showed the expected signals in duplicate: the protons of the group N-CH_3 showed a singlet, a deformed singlet or a double signal, integrating for three protons, in the interval δ = 3.65-3.78; the protons of the group CH_2-CO- showed, in each example, a double signal, integrating two protons, in the intervals δ = 3.75-3.99 (s, 1.1, 0.5H) and δ = 4.08-4.33 (s, 0.9, 1.5H). A similar behaviour was observed with the signals for the protons of the groups NH and H-3 (see experimental).

Compounds **6** were treated with acyl (acetyl, benzoyl) chlorides and triethylamine in order to induce cyclization to compounds **7**. However, this reaction was not observed,

Scheme 3



but several other new compounds were isolated and characterized.

Compound **6a** treated with acetyl chloride/triethylamine and the isolated crude product recrystallized from 2-propanol give **8**, characterized by elemental analysis and spectral (ir, ^{1}H-nmr) data. Particularly, the ^{1}H-nmr spectra showed signals at δ = 7.32 (s, 1H) and δ = 6.05 (s, 1H) assigned to H-3 and Ha, respectively.

Compounds **9b,c,d,f,g** treated in a similar way and the isolated crude products recrystallized from 2-propanol give compounds **10b,c,d,f,g**. However, due to the observed physical differences between the crude reaction products **9** and the compounds obtained after their recrystallization from 2-propanol, the ir and ^{1}H-nmr spectra of the crude products **9** were studied in detail.

The ir spectra of **9b,c,d,f,g** showed two carbonyl bands at about 1765-1780 cm^{-1} (s, C=O ester) and 1700-1710 cm^{-1} (s, C=O amide) and the ^{1}H-nmr spectra signals assignable to the protons Ha (δ = 6.33-6.36, s, 1H), H-3 (δ = 6.85-6.88, s, 1H) and N=CH (δ = 8.12-8.60, s, 1H). Therefore we propose that structure **9** is the correct one.

On the other hand, the compounds recrystallized from 2-propanol [10] showed in the ir spectra two carbonyl bands at about 1710-1720 cm^{-1} (s) and 1695-1710 (s) and in the ^{1}H-nmr spectra signals assigned to CH_2-CO (δ = 4.70-4.82, s, 2H) and H-3 (δ = 8.65-9.25, s, 1H). Therefore the structure **10** seems to us the correct one.

These interpretations of the results were further confirmed when compounds **10b,c** were boiled with hydrazine to give unequivocally **3a** (Scheme 1).

In summary, compounds **6b,c,d,f,g** treated with acelyl chloride/triethylamine give the respective **9** and boiling a solution of **9** in 2-propanol an intramolecular transposition takes place to give the corresponding **10**.

The reactions of **6b,c,d** with benzoyl chloride/triethylamine and **6e** with acetyl chloride/triethylamine were also studied. Unfortunately the ir and ^{1}H-nmr of the crude reaction products were not registered, and the crude products were recrystallized from 2-propanol. We obtained a new series of products for which the structure **11** seemed to us the most suitable. A similar product **11e** was obtained in the reaction of **6e** with acetyl chloride/triethylamine. The ir spectra of **11** showed two bands at about 1660-1740 cm^{-1} (s) and 1620-1690 cm^{-1} (s) for C=O, and the ^{1}H-nmr spectra showed singlets at δ = 4.13-4.82 (2H), δ = 6.40-7.08 (1H) and δ = 8.25-8.30 (1H) assigned to the protons of CH_2-CO, H-3 and CH=N. However, **11d** was a mixture of two isomers and gave two singlets for CH_2-CO (δ = 4.15, 1.4H and 4.75, 0.6H) and a deformed singlet (δ = 8.25) for H-3.

It seem reasonable to us to assume that the respective compounds **9** were also intermediates in the transformation of **6** to **11**. However, in these cases, for some reason, the acyl (benzoyl, acetyl) group of R_3-COO- were not transfered to the position 3 of the indole, but transesterified with 2-propanol to give the respective compounds **11b,c,d,e**.

We have also attempted the cyclization of the hydrazones **14**, (Scheme 3) to the [1,2]diazepino[4,5-*b*]indole derivatives **15**, with acetyl chloride/triethylamine, through a possible reaction similar to that reported [6,7] for the cyclization of 3-indolecarbohydrazones to pyridazino[4,5-*b*]indole derivatives.

The new compounds **14** were prepared by standard procedures [8] and characterized by elemental analysis and spectral data (ir, ^{1}H-nmr). The ir spectra of these compounds showed bands at about 1720-1725 cm^{-1} (s) and 1600-1610 cm^{-1} (s) for C=O and C=N; the ^{1}H-nmr spectra showed signals at δ = 3.53-3.78 (s, 0.8H) and δ = 3.93-4.27 (s, 1.2H) for CH_2-CO; δ = 11.20-11.35 (s, 0.6H) and δ = 11.40-11.60 (s, 0.4H) for -CONH -C(OH)=N; and δ = 11.0-11.8 (bs) for the indole-NH. In solution (DMSO-d_6) these compounds are mixtures of the two tautomeric forms -CONH- ⇌ -C(OH)=N-.

The treatment of **14** with acetyl chloride/triethylamine gave **16**, but not **15**. Compounds **16** were characterized by analytical and spectral data (ir, ^{1}H-nmr). Their ir spectra showed bands at about 1765-1775 cm^{-1} (s) and 1700-1710 cm^{-1} (s) for CO ester and amide respectively; their ^{1}H-nmr spectra showed singlets at δ = 6.40-6.78 (1H) for Ha, δ = 8.17-8.20 (1H) and δ = 7.73-8.04 for N=CH and H-2. Other signals of these spectra are detailed under the experimental.

EXPERIMENTAL

Melting points were determined in a Kofler apparatus and they are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 2-3 hours, at about 60-70°). Their spectra were recorded on a Perkin-Elmer 681 apparatus, using potassium bromide tablets for solid products and placing the products between crystals of sodium chloride for liquid products; the frequences were expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a Perkin-Elmer R-32 (90 MHz) instrument, with TMS as the internal reference, at a concentration of about 0.1 g/ml and solvent as indicated; the chemical shifts are reported in ppm from TMS and are given in δ units.

Thin-layer chromatography (tlc) was carried out on silicagel (DSF-5, Cammaga 0.3 mm. thickness) with benzene: dioxane: acetic acid (90:25:4) as solvent and the plates were scanned under ultraviolet light, λ = 254 and 366 nm.

The starting compounds **1** (mp 46-48°) and **5** (mp 126-128°), and **13** (mp 140-141°) were prepared by reported methods [2] and [8,9] respectively.

Ethyl 2(3-Acyl-1-methylindole)acetates **2**.

Compound **2a**.

This compound (mp 111-112°, 85%) was obtained by a reported method [2].

Compounds **2b-2d**.

These compounds were obtained according to the following general procedure.

The reactions were carried out in a 500 ml, three-neck round bottom flask with magnetic stirring, thermometer, dropping funnel and a reflux-condenser fitted with an anhydrous calcium chloride drying tube. To an ice-cooled solution of the corresponding amide (*N,N*-dimethylacetamide, -benzamide or -p-chlorobenzamide, 3 mmoles) in dry dioxane (10 ml), phosphous oxychloride (1.53 g, 10 mmoles) was slowly added dropwise during about 30 minutes. The cooling-bath was removed and the yellow coloured solution stirred for 1 hour at room temperature. The mixture was cooled again in an ice-bath and a solution of compound **1** (2.16 g, 10 mmoles) in dry dioxane (5 ml) was added dropwise during about 45 minutes so that the temperature of the reaction mixture was maintained at 8-10°. Then, the mixture was warmed in a water-bath for 3 hours at about 60°. The yellow-red coloured solution was cooled and slowly poured over crushed ice. The solution was neutralized (*p*H about 8) with stirring by addition of a solution of sodium hydroxide (19 g) in water (100 ml) and then just warmed to boiling, and finally cooled for 10 hours in a refrigerator. The crystalline product was collected by filtration, and thoroughly washed, first with cold water (5 × 20 ml) and then with warm water (5 × 20 ml) and finally recrystallized. In this way the following compounds were obtained.

Compound **2a**.

This compound was obtained from *N,N*-dimethylformamide, yield about 85%, mp 111-112° (ethanol); ir (potassium bromide): 1730 (s), 1660 (s), C=O, 735 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 1.20 (t, 3H, C-CH_3), 3.75 (s, 3H, N-CH_3), 4.80 (q, 2H, O-CH_2), 4.45 (s, 2H, CH_2), 7.2-7.68 (m, 3H, H-5, H-6, H-7), 7.9-8.1 (m, 1H, H-4), 10.20 (s, 1H, CHO).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.75; H, 6.18; N, 5.52.

Compound **2b**.

This compound was obtained from *N,N*-dimethylacetamide, yield about 75%, mp 116° (2-propanol); ir (potassium bromide): 1720 (s), 1640 (s), C=O, 725 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 35°): 1.22 (t, 3H, CH_3), 2.60 (s, 3H, CH_3-CO), 3.72 (s, 3H, N-CH_3), 4.12 (q, 2H, CH_2-O), 4.40 (s, 2H, CH_2-CO), 7.12-7.42 (m, 2H), 7.52-7.62 (m, 1H), 7.80-8.00 (s, 1H) for H-4, H-5, H-6, H-7.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.32; H, 6.24; N, 5.55.

Compound **2c**.

This compound was obtained from *N,N*-dimethylbenzamide, yield about 85%, mp 168-170° (ethanol); ir (potassium bromide): 1720 (s), 1710 (s), 1620 (s), C=O, 710 (s), 750 (m, aromatic monosubst), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (carbon tetrachloride): 1.27 (t, 3H, CH_3), 3.75 (s, 3H, N-CH_3), 4.15 (q, 2H, CH_2-O), 4.25 (s, 2H, CH_2-CO), 6.90-7.80 (m, 9 aromatic H).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.47; H, 6.02; N, 4.34.

Compound **2d**.

This compound was obtained from *N,N*-dimethyl-*p*-chlorobenzamide, yield about 65%, mp 156-158° (2-propanol); ir (potassium bromide): 1725 (s), 1620 (s), C=O, 740 (s, 1,2-aromatic disubst), 840 (s, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 1.17 (t, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.15 (q, 2H, CH_2-O), 4.30 (s, 2H, CH_2-CO), 6.95-7.25 (m, 4H), 7.35-7.65 (m, 4H) for aromatic protons.

Anal. Calcd. for $C_{20}H_{18}ClNO_3$: C, 67.52; H, 5.06; N, 3.94. Found: C, 67.66; H, 5.11; N, 3.73.

4,5-Dihydro-6-methyl-4-oxo-3*H*[1,2]diazepino[5,6-*b*]indoles **3**.

A solution of the corresponding compound **2** (5 mmoles) and hydrazine hydrate (8 mmoles) in ethanol (50 ml) was boiled for 1 hour. Solvent was removed in a rotavapor, the residual material suspended in water, and the solid collected by filtration, washed with water and recrystallized. In this way the following compounds were obtained:

Compound **3a**.

This compound was obtained from **2a**, yield about 90%, mp 167-168° (2-propanol); ir (potassium bromide): 3280 (bs, NH), 1660 (s, C=O), 1610 (m, C=N), 730 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 35°): 3.60 (s, 3H, N-CH_3), 6.20 (s, 1H, OH), 6.25 (s, 1H, H-5), 7.10-7.55 (m, 3H, H-7, H-8, H-9), 7.95-8.10 (m, 1H, H-10), 8.70 (s, 1H, H-1). The signal for OH disappears by addition of deuterium oxide.

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.42; H, 5.20; N, 19.60.

Compound **3b**.

This compound was obtained from **2b**, yield about 87%, mp 245° (2-propanol); ir (potassium bromide): 3300 (m), 3200 (m), NH, 1700 (s, C=O), 1600 (s, C=N), 750 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 90°): 2.88 (s, 3H, CH_3), 3.48 (s, 3H, N-CH_3), 6.00 (s, 1H, H-5), 7.00-7.40 (m, 3H), 7.65-7.85 (m, 1H, H-10); ^{1}H-nmr (trifluoroacetic acid): 3.30 (s, 1H, CH_3), 3.90 (s, 1H, N-CH_3), 7.02 (s, 1H, H-5), 7.40-7.75 (m, 3H), 8.05-8.25 (m, 1H, H-10).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.88; H, 5.90; N, 18.71.

Compound **3c**.

This compound was obtained from **2c**, yield about 95%, mp 192-194° (ethanol); ir (potassium bromide): 3200 (m, NH), 1650 (s, C=O), 1600 (s, C=N), 750 (s, 1,2-aromatic disubst), 710 (s), 750 (m, aromatic monosubst); ^{1}H-nmr (deuteriochloroform): 3.05 (s, 3H, N-CH_3), 4.30-5.40 (bs, 2H, NH, OH), 5.95 (s, 1H, H-5), 6.40-7.90 (m, 4H), 7.50 (s, 5H, C_6H_5). The broad signal for NH and OH disappears by addition of deuterium oxide.

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.71; H, 4.53; N, 14.50.

Compound **3d**.

This compound was obtained from **2d**, yield about 85%, mp 225-227° (2-propanol); ir (potassium bromide): 3260 (m), 3170 (m), NH; 1650 (s, C=O) 1600 (m, C=N), 740 (m, 1,2-aromatic disubst), 820 (m, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 3.52 (s, 3H, N-CH_3), 5.68 (s, 1H, OH), 6.22 (s, 1H, H-5), 6.40-7.70 (m, 8H) for indole and *p*-Cl-C_6H_4. The signal for OH disappears by addition of deuterium oxide.

Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98. Found: C, 66.58; H, 4.26; N, 12.85.

4-Acetoxy-3-acetyl-6-methyl-3*H*[1,2]diazepino[5,6-*b*]indoles **4**.

To a solution of the respective compound **3** (3 mmoles) in dried pyridine (8 ml), acetic acid anhydride (3 ml) was added. The mixture was warmed for 0.5 hours in a water bath, then poured on crushed ice and the precipitate collected and recrystallized.

Compound **4a**.

This compound was obtained from **3a**, yield about 95%, mp 195-196° (from ethanol); ir (potassium bromide): 1730 (s, C=O acetoxy), 1670 (s, C=O amide), 1620 (s, C=N), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.45 (s, 6H, 2CH_3-CO), 3.52 (m, 3H, CH_3-N), 6.20 (s, 1H, H-5), 7.04-7.70 (m, 4H, H-7, H-8, H-9, H-10), 7.90 (s, 1H, H-1).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.44; H, 5.11; N, 13.98.

Compound **4d**.

This compound was obtained from **3d**, yield about 93%, mp 209-210° (ethanol); ir (potassium bromide): 1740 (s, C=O acetoxy), 1660 (s, C=O amide), 1600 (s, C=N), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform/trifluoroacetic acid): 2.34 (s, 6H, 2CH_3-CO), 3.70 (s, 3H, CH_3-N), 6.75 (s, 1H, H-5), 6.50-7.80 (m, 8 aromatic protons).

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 62.25; H, 5.19; N, 10.90. Found: C, 62.32; H, 5.08; N, 10.83.

2-(1-Methylindole)acetohydrazones **6**.

To a solution of **2** (1.0 g, 4.9 mmoles) in ethanol (20 ml) and excess of

the respective aldehyde or ketone (7-8 mmoles) was added. The reaction mixture was boiled for 20-30 minutes, the solvent partially removed *in vacuo* and the crystalline hydrazone collected by filtration. The following compounds were prepared:

Compound **6a**.

This compound was obtained from acetaldehyde, yield about 90%, mp 173-174° (ethanol); ir (potassium bromide): 3200 (s, NH), 1660 (s, C=O, C=N), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 35°): 1.80 (d, ~1.6H), 1.90 (d, ~1.4H) for N=C(CH_3), 3.65 (s, ~1.6H), 3.68 (s, ~1.4H) for N-CH_3, 3.75 (s, ~1.1H), 4.08 (s, ~0.9H) for CH_2, 6.32 (ds, 1H, H-3), 6.80-7.15 (m, 2H indole), 7.15-7.55 (m, 3H, 2H indole and N=CH), 11.2 (bs, ~0.6H), 11.4 (bs, ~0.4H) for NH. These signals for NH disappear by addition of deuterium oxide.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.78; H, 6.72; N, 18.34.

Compound **6b**.

This compound was obtained from benzaldehyde, yield about 95%, mp 219-220° (ethanol); ir (potassium bromide): 3200 (m, NH), 1670 (s, C=O), 1650 (s, C=N), 745 (s, 1,2-aromatic disubst), 690 (s), 735 (s, aromatic monosubst); ^{1}H-nmr (DMSO-d_6, 35°): 3.70 (s, ~1.8H), 3.73 (s, ~1.2H) for N-CH_3, 3.85 (s, ~0.8H), 4.26 (s, ~1.2H) for CH_2, 6.33 (ds, 1H, H-3), 6.80-7.25 (m, 2H indole), 7.25-8.25 (m, 8H, 2H indole, N=CH, C_6H_5), 11.5 (bs, ~0.6H), 11.65 (bs, ~0.4H) for NH. The signals for NH disappear by addition of deuterium oxide.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 74.25; H, 6.05; N, 14.48.

Compound **6c**.

This compound was obtained from *p*-chlorobenzaldehyde, yield about 95%, mp 219-220° (2-propanol); ir (potassium bromide): 3180 (m, NH), 1670 (s, C=O, C=N), 740 (s, 1,2-aromatic disubst), 820 (m, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 3.70 (ds, 3H, N-CH_3), 3.88 (ds, ~0.7H), 4.29 (ds, ~1.3H) for CH_2, 6.35 (ds, 1H, H-3), 6.85-7.25 (m, 2H indole), 7.25-8.30 (m, 7H, 2H indole, N=CH, 4H of *p*-chlorophenyl), 11.60 (bs, ~0.7H), 11.75 (bs, ~0.3H) for NH. The signals for NH disappear by addition of deuterium oxide.

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.30; H, 4.95; N, 12.90. Found: C, 66.60; H, 4.74; N, 12.84.

Compound **6d**.

This compound was obtained from piperonal, yield about 90%, mp 212-213° (2-propanol); ir (potassium bromide): 3200 (m, NH), 1670 (s, C=O, C=N), 740 (s, 1,2-aromatic disubst), 805 (m, 1,2,4-aromatic trisubst); ^{1}H-nmr (DMSO-d_6, 35°): 3.72 (s, 3H, N-CH_3), 3.83 (s, 0.6H), 4.25 (s, 1.4H), CH_2-CO, 6.05 (s, 2H, O-CH_2-O), 6.34 (s, ~0.7H), 6.37 (s, ~0.3H) for H-3, 6.75-7.55 (m, 6H, H-4, H-5, H-6, H-7 of indole, H-2′ and H-5′ of piperonyl), 7.35 (bs, 1H, N=CH); 8.05 (d, 1H, H-6′), 11.45 (s, ~0.7H), 11.52 (s, ~0.3H), NH).

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.82; H, 5.11; N, 12.55.

Compound **6e**.

This compound was obtained from acetophenone yield about 97%, mp 188-189° (2-propanol); ir (potassium bromide): 3190 (s, NH), 1680 (s, C=O, C=N), 750 (s, 1,2-aromatic disubst), 700 (s), 770 (s, aromatic monosubst); ^{1}H-nmr (DMSO-d_6, 35°): 2.32 (s, 3H, CH_3), 3.71 (s, 3H, N-CH_3), 3.99 (s, ~0.7H), 4.33 (s, ~1.3H), CH_2, 6.37 (s, 1H, H-3), 6.87-7.25 (m, 2H indole), 7.25-7.57 (m, 2H indole + H-3′, H-4′, H-5′), 7.67-7.92 (m, 2H, H-2′, H-6′).

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.74; H, 6.53; N, 13.64.

Compound **6f**.

This compound was obtained from *o*-chlorobenzaldehyde, yield about 95%, mp 210-212° (2-propanol); ir (potassium bromide): 3190 (w, NH), 1675 (s, C=O, C=N); 745 (s), 750 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 37°): 3.78 (s, 3H, CH_3), 3.93 (s, ~0.5H), 4.30 (s, ~1.5H, CH_2), 6.49 (s, 1H, H-3), 7.00-8.40 (m, 9H, CH=N, indole and *o*-chlorophenyl), 9.50 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.30; H, 4.95; N, 12.90. Found: C, 66.40; H, 4.72; N, 12.70.

Compound **6g**.

This compound was obtained from *o*-nitrobenzaldehyde, yield about 90%, mp 183-184° (2-propanol); ir (potassium bromide): 3200 (m, NH), 1670 (s, C=O, C=N), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 3.70 (s, 3H, N-CH_3), 4.28 (s, 2H, CH_2-CO), 6.35 (s, 1H, H-3), 6.95-8.10 (m, 8H, aromatic), 8.95 (s, 1H, HC=N), 12.00-12.20 (d, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.15; H, 4.73; N, 16.81.

Products from the Reactions of **6** with Acyl Halides and Triethylamine.

General Procedure.

The reactions were carried out in a 250 ml three-neck round bottom flask, provided with magnetic stirring, thermometer, dropping funnel and a reflux-condenser with an anhydrous calcium chloride drying tube. To a stirred suspension of the corresponding hydrazone **2** (3 mmoles, dried *in vacuo* over phosphorus pentoxide) in dried ethyl acetate (75 ml), dried triethylamine (10 ml, freshly distilled) was added at room temperature. Acetyl chloride (5 ml, freshly distilled) in dry ethyl acetate (15 ml) was slowly dropped into the suspension, maintaining the temperature below 40°. Stirring was continued at room temperature until tlc showed that the reaction was complete (about 3 hours). The precipitate of triethylamine hydrochloride was collected by filtration, washed with ethyl acetate and decolorized. The combined filtrates were washed successively with water, saturated solution of sodium bicarbonate and water. The solution was dried with anhydrous sodium sulfate and filtered, the solvent removed *in vacuo* and the crude solid product collected. When benzoyl chloride (compounds **11b**, **11c**, **11d**) was the reagent, chloroform was used as the solvent, instead of ethyl acetate, in order to avoid a possible reaction of transesterification.

In this way the following compounds were obtained:

Compound **8**.

This compound was obtained from **6a** and acetyl chloride/triethylamine, mp 138-140° (from 2-propanol), yield about 30%; ir (potassium bromide): 3290 (s, NH), 1730 (s, C=O), 1685 (s, C=N), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 37°): 1.12 (d, 3H, CH_3), 2.65 (s, 3H, CH_3-CO), 3.53 (s, 3H, N-CH_3), 6.05 (s, 1H, Ha), 7.02-7.42 (m, 4H, N=CH, H-5, H-6, H-7), 7.32 (s, 1H, H-3), 7.82 (d, 1H, H-4, $J_{4,5}$ = 6 Hz), 10.92 (s, 1H, NH). This last signal disappears by addition of deuterium oxide.

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.50; H, 6.35; N, 15.05.

Compound **9b**.

This compound was obtained from **6b** and acetyl chloride/triethylamine. The crude product obtained according to the general procedure had mp 166°; ir (potassium bromide): 1770 (s, CO ester), 1700 (s, CO amide), 740 (s, 1,2-aromatic disubst), 690 (s, aromatic monosubst); ^{1}H-nmr (deuteriochloroform): 2.13 (s, 3H, CH_3-CON), 2.55 (s, 3H, CH_3-COO), 3.71 (s, 3H, CH_3-N), 6.36 (s, 1H, Ha), 6.88 (s, 1H, H-3), 7.00-7.80 (m, 9H, H-4, H-5, H-6, H-7 and C_6H_5), 8.18 (s, 1H, N=CH).

Compound **10b**.

This compound was obtained when compound **9b** was recrystallized from 2-propanol, mp 158-160°, yield about 70% from **6b**; ir (potassium bromide): 1720 (s), 1710 (s), C=O, 1640 (s, C=N); 750 (s), 690 (s, aromatic monosubst), 740 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.55 (s, 3H), 2.70 (s, 3H for 2 CH_3-CO), 3.76 (s, 3H, N-CH_3); 4.82 (s, 2H, CH_2-CO), 7.20-7.55 (m, 6H), 7.70-8.00 (m, 3H), 8.65 (s, 1H, N=CH).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.10; H, 5.90; N, 11.32.

Compound **9c**.

This compound was obtained from **6c** and acetyl chloride/triethylamine. The crude product obtained according to the general procedure had mp 147°; ir (potassium bromide): 1780 (s, CO ester), 1700 (s, CO amide), 740 (s, 1,2-aromatic disubst), 820 (s, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6, 35°): 2.21 (s, 3H, CH_3-CON), 2.50 (s, 3H, CH_3-CO), 3.70 (s, 3H, N-CH_3), 6.33 (s, 1H, Ha), 6.85 (s, 1H, H-3), 7.00-7.70 (m, 8H), 8.12 (s, 1H, N=CH).

Compound **10c**.

This compound was obtained when compound **9c** was recrystallized from 2-propanol, mp 158-160°, yield about 78% from **6c**; ir (potassium bromide): 1700 (s), 1695 (s), C=O, 1650 (s, C=N), 740 (s, 1,2-aromatic disubst), 820 (m, 1,4-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.55 (s, 3H), 2.70 (s, 3H), CH_3-CO, 3.78 (s, 3H, N-CH_3), 4.80 (s, 2H, CH_2-CO), 7.20-7.60 (m, 5H), 7.60-7.95 (m, 3H), 8.68 (s, 1H, N=CH).

Anal. Calcd. for $C_{22}H_{20}ClN_3O_3$: C, 62.25; H, 5.19; N, 10.90. Found: C, 61.98; N, 4.98; N, 11.00.

Compound **10d**.

This compound was obtained from **6d** and acetyl chloride/triethylamine according to the general procedure and the crude product recrystallized from 2-propanol, mp 163-164°, yield about 65%; ir (potassium bromide): 1700 (s), 1650 (s) C=O, 740 (s, 1,2-aromatic disubst), 840 (m), 870 (w, 1,2,4-aromatic trisubst); ^{1}H-nmr (deuteriochloroform): 2.58 (s, 3H), 2.72 (s, 3H) for 2CH_3-CO, 3.78 (s, 3H, N-CH_3), 4.70 (s, 2H, CH_2-CO), 6.03 (s, 2H, CH_2O_2), 6.80-7.60 (m, 7H), 7.75-7.95 (m, 1H), 8.47 (s, 1H, N=CH).

Anal. Calcd. for $C_{23}H_{21}N_3O_5$: C, 66.88; H, 5.07; N, 10.02. Found: C, 66.63; H, 5.06; N, 10.32.

Compound **9f**.

This compound was obtained from **6f** and acetyl chloride/triethylamine accoring to the above general procedure. The crude product had mp 170°; ir (potassium bromide): 1770 (s, C=O ester), 1710 (s, C=O amide), 760 (s), 750 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.21 (s, 3H, CH_3-CON), 2.50 (s, 3H, CH_3-COO), 3.69 (s, 3H, N-CH_3), 6.33 (s, 1H, Ha), 6.88 (s, 1H, H-3), 7.05-7.65 (m, 7H), 7.80-8.05 (m, 1H), 8.60 (s, 1H, N=CH).

Compound **10f**.

This compound was obtained when compound **9f** was recrystallized from 2-propanol, mp 153-154°; ir (potasium bromide): 1710 (s), 1700 (s), 1640 (s), C=O, 765 (m), 750 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.56 (s, 3H), 2.68 (s, 3H) for 2 CH_3-CO, 3.75 (s, 3H, N-CH_3), 4.77 (s, 2H, CH_2-CO), 7.13-7.53 (m, 6H), 7.73-8.13 (m, 2H), 9.06 (s, 1H, N=CH).

Anal. Calcd. for $C_{22}H_{20}ClN_3O_3$: C, 62.25; H, 5.19; N, 10.90. Found: C, 62.12; H, 5.04; N, 10.79.

Compound **9g**.

This compound was obtained from **6g** and acetyl chloride/triethylamine by the above described general procedure. The crude product showed mp 207°; ir (potassium bromide): 1765 (s, C=O, ester), 1705 (s, C=O amide), 735 (s), 750 (s, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.25 (s, 3H, CH_3-CON), 2.49 (s, 3H, CH_3-COO), 3.70 (s, 3H, N-CH_3), 6.35 (s, 1H, Ha), 6.70-8.40 (m, 9H), 8.60 (s, 1H, N=CH).

Compound **10g**.

This compound was obtained when compound **9g** was recrystallized from 2-propanol, mp 148-150°; ir (potassium bromide): 1715 (s), 1710 (s), 1635 (s), C=O, 735 (m), 740 (m, 1,2-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.55 (s, 3H), 2.69 (s, 3H) for 2 CH_3-CO, 3.77 (s, 3H, N-CH_3), 4.88 (s, 2H, CH_2-CO), 7.30-8.40 (m, 8H), 9.25 (s, 1H, N=CH).

Anal. Calcd. for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.55; H, 4.61; N, 13.48.

Compound **3a** from **10**.

A solution of the respective compound **10b** or **c** (2 mmoles), 90% hydrazine hydrate (10 mmoles) and 2-propanol (10 ml) was boiled for 1 hour. The solvent was removed in vacuum and the residual material diluted with water. The solid was collected and recrystallized to give **3a**, mp 167-168° (2-propanol), identical to the above described compound (ir, ^{1}H-nmr).

Compound **11b**.

This compound was obtained from **6b** and benzoyl chloride/triethylamine according to the above described general procedure and the crude product recrystallized from 2-propanol, mp 148-150°, yield about 70%; ir (potassium bromide): 1660 (m), 1620 (s), C=O, 740 (s, 1,2-aromatic disubst), 760 (s), 750 (s, aromatic monosubst); ^{1}H-nmr (DMSO-d_6): 3.70 (s, 3H, N-CH_3), 4.13 (s, 2H, CH_2-CO), 6.42 (s, 1H, H-3), 6.80-7.60 (m, 13H), 7.70-7.95 (m, 2H).

Anal. Calcd. for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.80; H, 5.15; N, 10.54.

Compound **11c**.

This compound was obtained from **6c** and benzoyl chloride/triethylamine according to the above described general procedure, and the crude product recrystallized from 2-propanol, mp 112-114° yield about 60%; ir (potassium bromide): 1730 (s), 1650 (s), C=O, 740 (s, 1,2-aromatic disubst), 700 (s), 735 (m, aromatic monosubst), 820 (m, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 4.82 (s, 3H, N-CH_3), 4.82 (s, 2H, CH_2-CO), 7.08 (s, 1H, H-3), 7.35-8.00 (m, 13H), 8.30 (s, 1H, N=CH).

Anal. Calcd. for $C_{25}H_{20}ClN_3O_2$: C, 71.06; H, 4.82; N, 9.56. Found: C, 70.80; H, 4.76; N, 9.14.

Compound **11d**.

This compound was obtained from **6d** and benzoyl chloride/triethylamine according to the above described general procedure, and the crude product recrystallized from 2-propanol, mp 164-166°, yield about 70%; ir (potassium bromide): 1710 (s), 1670 (s), C=O, 1625 (s), C=N, 740 (m, 1,2-aromatic disubst), 820 (m, 1,2,4-aromatic trisubst), 700 (m), 750 (m, 1,2-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 3.72 (s, 2.1H), 3.82 (s, 0.9H), N-CH_3, 4.15 (s, 1.4H), 4.75 (s, 0.6H), CH_2-CO, 6.04 (s, 1.4H), 6.11 (s, 0.6H), 6.40 (ds, 1H, H-3), 7.00-8.00 (m, 12H), 8.25 (ds, 1H, N=CH). The compound is a mixture of the two isomeric hydrazones.

Anal. Calcd. for $C_{26}H_{21}N_3O_4$: C, 69.84; H, 4.69; N, 7.44. Found: C, 70.19; H, 4.59; N, 7.71.

Compound **11e**.

This compound was obtained from **6e** and acetyl chloride/triethylamine according to the general procedure and the crude product recrystallized from 2-propanol, mp 113-115°, yield about 60%; ir (potassium bromide): 1710 (s), 1690 (s), C=O, 740 (s, 1,2-aromatic disubst), 690 (m), 750 (s), aromatic monosubst; ^{1}H-nmr (deuteriochloroform): 1.98 (s, 3H, CH_3), 2.51 (s, 3H, CH_3-CO), 3.60 (s, 3H, N-CH_3), 4.29 (s, 2H, CH_2-CO), 6.41 (s, 1H, H-3), 7.00-7.40 (m, 3H), 7.40-7.70 (m, 4H), 7.75-8.00 (m, 1H). A similar spectra was obtained with DMSO-d_6 as the solvent.

Compound **12**.

A mixture of **10f**, ethanol (50 ml) and 10% aqueous solution of sodium hydroxide (2 ml) was stirred for 24 hours at room temperature. Most of the solvent was removed *in vacuo* and the residual material diluted with water and extracted with ethyl acetate. The extract was washed successively with saturated solution of sodium chloride and water, dried on sodium sulfate, solvent removed *in vacuo* and the residual solid recrystallized, mp 240° (from ethanol); ir (potassium bromide): 3190 (w), 3100 (s), NH, 1675 (s), 1660 (s), C=O, 1600 (s, C=N), 735 (s, 1,2-aromatic disubst), 810 (m, 1,4-aromatic disubst); ^{1}H-nmr (deuteriochloroform/trichloroacetic acid): 3.03 (s, 3H, CH_3-CO), 4.20 (s, 3H, N-CH_3), 4.52 (s, 2H, CH_2-CO), 7.25-8.10 (m, 8H), 8.28 (s, 1H, N=CH).

Anal. Calcd. for $C_{20}H_{18}ClN_3O_2$: C, 65.31; H, 4.90; N, 11.43. Found: C, 65.23; H, 4.81; N, 11.23.

3-Indoleacetohydrazones **14**.

These compounds were prepared from **13** in similar way as described above for **6**.

Compound **14a**.

This compound had mp 214-216° (from 2-propanol), yield about 98%; ir (potassium bromide): 3200 (s), 3310 (s), NH, 1725 (s, C=O), 1600 (m, C=N), 740 (s, 1,2-aromatic disubst), 830 (s, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 3.53 (s, 0.8H), 3.93 (s, 1.2H), CH_2-CO, 6.80-8.20 (m, 10H), 10.8 (bs, 1H, NH indol), 11.2 (s, 0.6H), 11.4 (s, 0.4H), for -CONH ⇌ C(OH)=N).

The signals for NH and OH disappear by the addition of deuterium oxide. The compound is a mixture of at least two isomers.

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.52; N, 13.48. Found: C, 65.70; H, 4.45; N, 13.22.

Compound **14b**.

This compound had mp 199-200° (from 2-propanol), yiel about 97%; ir (potassium bromide): 1720 (s, C=O), 1610 (m, C=N), 740 (s, 1,2-aromatic disubst), 820 (s, 1,4-aromatic disubst), 3200 (s), 3310 (s), NH; ^{1}H-nmr (DMSO-d_6): 2.50 (s, 3H, CH_3), 3.76 (s, 0.8H), 4.27 (s, 1.2H, CH_2-CO), 7.00-8.45 (m, 10H), 11.0 (bs, 1H, NH), 11.35 (s, 0.6H), 11.6 (s, 0.4H), for -CONH- ⇌ -C(OH)=N. The signals for OH and NH disappear by the addition of deuterium oxide. The compound is a mixture of at least two isomers.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.37; H, 6.15; N, 15.32.

Products from the reaction of **14** with acetyl chloride and triethylamine.

The respective compound **14** was treated with acetyl chloride and triethylamine, with ethylacetate as solvent, as we have above described for the reactions with compound **6**. The crude products were recrystallied from 2-propanol.

Compound **16a**.

This compound had mp 200°, yield about 21%; ir (potassium bromide): 1775 (s, C=O ester), 1700 (s, C=O amide), 740 (m, 1,2-aromatic disubst), 825 (m, 1,4-aromatic disubst); ^{1}H-nmr (DMSO-d_6): 2.28 (s), 2.45 (s), 2.65 (s), for 3 CH_3-CO , 6.78 (s, 1H, Ha), 7.30-7.80 (m, 3H, H-5, H-6, H-7), 7.50 (d, 2H), 7.78 (d, 2H), for -C_6H_4-Cl-*p*, 8.04 (s, 1H), 8.20 (s, 1H), for H-2 and N=CH, 8.30-8.45 (m, 1H, H-4).

Anal. Calcd. for $C_{23}H_{20}ClN_3O_4$: C, 63.10; H, 4.60; N, 9.59. Found: C, 62.90; H, 4.86; N, 9.73.

Compound **16b**.

This compound had mp 166-168°, yield about 34%; ir (potassium bromide): 1765 (s, C=O ester), 1710 (s, C=O amide), 750 (s, 1,2-aromatic disubst), 820 (s, 1,4-aromatic disubst); ^{1}H-nmr (deuteriochloroform): 2.18 (s, 3H), 2.37 (s, 3H), 2.52 (s, 3H), 2.65 (s, 3H), for -CH_3 and 3 CH_3-CO, 6.40 (s, 1H, Ha), 7.10-7.75 (m, 3H, H-5, H-6, H-7), 7.18 (d, 2H), 7.57 (d, 2H), for -C_6H_4-*p*, 7.73 (s, 1H), 8.17 (s, 1H) for H-2 and N=CH, 8.30-8.45 (m, 1H, H-4).

Anal. Calcd. for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.84; H, 5.92; N, 9.80.

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