# Synthesis of 3*H*[1,2]Diazepino[5,6-*b*]indole and 3*H*[1,2]Diazepino[4,5-*b*]indole Derivatives



A. Monge*, J. A. Palop, T. Goñi and A. Martinez

Facultad de Farmacia, Departamento de Química Orgánica y Farmaceutica, Universidad de Navarra, Pamplona, Spain

E. Fernández-Alvarez

Centro Nacional de Química Orgánica, C/Juan de la Cierva, No. 3, Madrid-6, Spain

Received July 19, 1983

The synthesis of two new derivatives of 3*H*[1,2]diazepino[5,6-*b*]indole, **5** and **11**, and one new derivative of 3*H*[1,2]diazepino[4,5-*b*]indole, **16**, are described. Compound **5** was obtained by the reaction of methyl 2-(3-methoxycarbonyl-1-methylindole)acetate **2**, with hydrazine. Compound **11** was obtained in two ways from ethyl 2-(1-methylindole)acetate (**8**) by formylation and reaction with hydrazine. Compound **16** was obtained treating 3-(2-ethoxycarbonylindole)acetonitrile (**14**) with hydrazine.

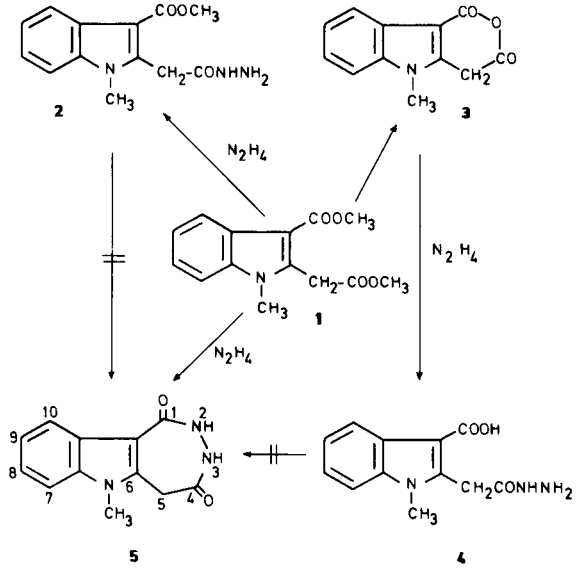
*J. Heterocyclic Chem.*, **21**, 381 (1984).

The benzodiazepines are a broad group of psychopharmacologic agents with particular interest in the treatment of anxiety and sleeping disorders [1]. During the last few years special attention has been drawn to the synthesis and study of the psychopharmacological properties of new diazepines with fused heterocyclic systems, such as pyrrole [2], thiophene [3], imidazole [4], pyrazole [5], isoxazole [6], quinoline [7], pyridine [8], and also indole [9], isoindole [10] and carbazole [11].

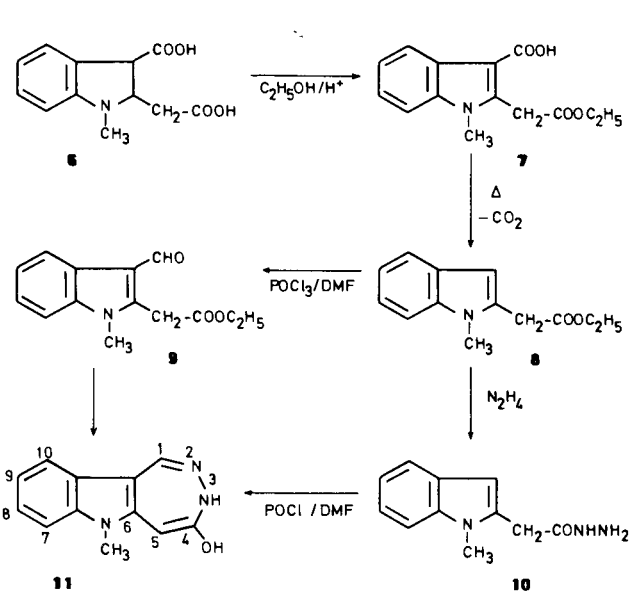
The chemistry of 1,2-diazepines has been recently reveiwed [12] and, to our knowledge, only two papers on [1,2]diazepinoindoles have been published [13,14], with reference to 1*H*[1,2]diazepino[4,5-*b*]indoles [13] and [1,2]diazepino[6,5,4-*cd*]indoles [14]. As a continuation to our previous work [13], this paper [15] describes the synthesis of three new compounds: two derivatives of 3*H*[1,2]diazepino[5,6-*b*]indole (compounds **5** and **11**) and one derivative of 3*H*[1,2]diazepino[4,5-*b*]indole (compound **16**).

Compound **5** was synthesized according to the Scheme 1, starting with the previously reported [16] compound **1**. Boiling this compound for 2 hours with 40% hydrazine hydrate in 2-propanol gave the monohydrazide **2** (53%) and the attempted cyclization of this compound in boiling toluene was not fruitful. On the other hand, boiling the previously reported [16] compound **3** for 4 hours with 40% hydrazine hydrate in ethyl alcohol gave the hydrazide **4** (78%), which similarly does not cyclize to **5**. When both compounds **1** or **3** were boiled with hydrazine hydrate at concentrations higher than 40%, without any solvent, the bis-hydrazide was obtained. Finally, boiling compound **1** for 36 hours with 40% hydrazine hydrate, without any sol-

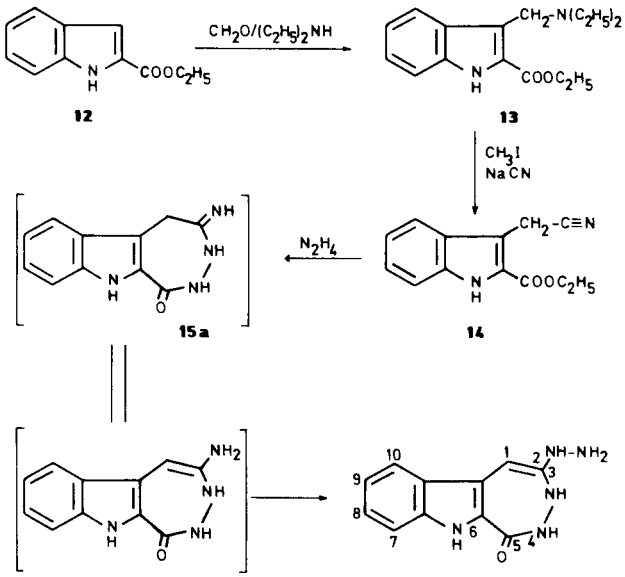
Scheme 1



Scheme 2



Scheme 3



vent, compound **5** (58%) was obtained. The structure of the above mentioned compounds was determined by elemental and spectro-analytical data; in particular, the ir spectra of **2** shows the 1690 $cm^{-1}$ band for the carbonyl group of an aliphatic ester, but not the 1740 $cm^{-1}$ band for the carbonyl group of an aromatic ester, both of them observed with compound **2**.

Compound **11** (Scheme 2) was synthesized from the previously reported [15] compound **6** in two ways. Boiling this last compound with ethanol/hydrochloric acid for 20 minutes gave the mono ester **7** (70%), which was thermally decarboxylated to **8** (70%) and then the hydrazide **10** was prepared (80%). Formylation of **8** and **10** by the Vilsmeier-Haack reaction gave the compounds **9** (80%) and **11** (90%), respectively. Alternatively, boiling compound **9** for 1 hour with hydrazine hydrate in ethyl alcohol also gave **11** (90%). The structure of compounds **6-11** was determined by elemental and spectro-analytical data; in particular, the $^1$H-nmr spectra of **11** did not show any signal for a $-CH_2-C(=O)-$ group, and so the structure of **11** was supported by this and other spectral data. Compound **16** was synthesized as illustrated in Scheme 3. Compound **12** under Mannich reaction conditions gave **13** (90%) which in quaternization with methyl iodide and treatment with sodium cyanide in a one-pot synthesis gave **14** (40%). When this last compound was boiled with hydrazine hydrate in ethanol, **16** (70%) was obtained. Scheme 3 also shows the probable course of this last reaction.

## EXPERIMENTAL

Melting points were determined with a Kofler melting point apparatus and 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°). The ir spectra were recorded on a Perkin-Elmer 681 apparatus using potassium bromide pellets for solid products and placing the products between sodium chloride plates for liquid products. The frequencies are 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 with solvents as indicated. The chemical shifts are reported in ppm from TMS as an internal standard and are given in $\delta$ units.

The thin-layer chromatography (tlc) was carried out on silica-gel (DSF-5 Cammag, 0.3 mm thickness) with benzene:dioxane:acetic acid, 90:25:4 (v/v) as the solvent and the plates were scanned under ultraviolet light, $\lambda$ = 254 and 366 nm.

The following starting materials were prepared by previously reported methods: methyl 2-(3-methoxycarbonyl-1-methylindole)acetate (**1**), mp 100° [16], 2-(3-carboxy-1-methylindole)acetic acid (**6**), mp 261° [17], 2-(3-carboxy-1-methylindole)acetic anhydride (**3**), mp 252° [17].

2-(3-Methoxycarbonyl-1-methylindole)acetohydrazide (**2**).

Compound **1** (5.2 g, 20 mmoles) in 2-propanol (50 ml) and 40% hydrazine hydrate (20 ml), were refluxed for 22 hours. The reaction mixture was cooled. Hydrazine and 2-propanol were removed *in vacuo*. The residual material was collected by filtration and crystallized from 2-propanol to give **2** (2.6 g, 53%), as white-yellow needles, mp 212-213°; ir: 3300, 1690, 1640; $^1$H-nmr (DMSO-$d_6$): $\delta$ 3.75 (s, N-$CH_3$, 3H), 3.85 (s, O-$CH_3$, 3H), 4.21 (s, $CH_2$, 2H), 7.15-7.7 (m, $H_{5,6,7}$, 3H), 7.9-8.1 (m, $H_4$, 1H), 9.15 (bs, NH, 1H).

*Anal.* Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.33; H, 5.45; N, 15.97.

2-(3-Carbethoxy-1-methylindole)acetohydrazide (**4**).

Compound **3** (1.1 g, 5 mmoles), dissolved in ethanol (10 ml) and 40% hydrazine hydrate (10 ml) were refluxed for 4 hours. The reaction mixture was cooled and the ethanol removed *in vacuo*. The residual material was collected by filtration, washed with water and crystallized from ethanol/DMF to give **4** (0.9 g, 78%) as white needles, mp 124-125°; ir: 3300-3050, 1710, 1670; $^1$H-nmr (DMSO-$d_6$): 3.75 (s, $CH_3$, 3H), 4.21 (s, $CH_2$, 2H), 7.1-7.65 (m, $H_{5,6,7}$, 3H), 7.9-8.1 (m, $H_4$, 1H).

*Anal.* Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.77; H, 5.42; N, 17.13.

1,2,4,5-Tetrahydro-1,4-dioxo-3*H*[1,2]diazepino[5,6-*b*]indole (**5**).

Compound **1** (2.1 g, 8 mmoles) and 40% hydrazine hydrate (20 ml) was refluxed for 36 hours. Most of the hydrazine was removed *in vacuo*. The residual material was collected by filtration, washed with water and the solid crystallized from methanol to give **5** (1.1 g, 58%) as yellow needles, mp 239-240°; ir: 3320, 1705, 1650; $^1$H-nmr (DMSO-$d_6$): 3.75 (s, $CH_3$, 3H), 4.35 (s, $CH_2$, 2H), 7.2-7.8 (m, $H_{5,6,7}$, 3H), 8.0-8.15 (m, $H_4$, 1H), 4.3-5.3 (bs, NH, 2H).

*Anal.* Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found; C, 62.98; H, 4.71; N, 18.74.

Ethyl 2-(3-Carboxy-1-methylindole)acetate (**7**).

A solution of **6** (4.66 g, 20 mmoles) in dry ethanol/hydrochloric acid (100 ml, 0.5%) was heated under reflux for 20 minutes upon cooling, a precipitate separated which was collected and dried to give **7** (3.65 g, 70%) as white crystals, mp 202-203° (lit [17] mp 202-203°).

Ethyl 2-(1-Methylindole)acetate (**8**).

Compound **7** (2.6 g, 10 mmoles) was heated under nitrogen at 190-210°, until gas evolution ceased. The residue was distilled to give **8** (1.5 g, 70%) as a colorless oil, bp 85-90° (0.025 mm Hg) lit [17] bp 195-250° (0.2 mm Hg). Upon cooling, a white solid, mp 46-48° was obtained.

Ethyl 2-(3-Formyl-1-methylindole)acetate (**9**).

In a 500 ml three necked round bottom flask, with mechanical stirring

and protected with a tube of anhydrous calcium chloride, freshly distilled *N,N*-dimethylformamide (DMF, 45 ml) was cooled (20-30 minutes) in an ice-bath. From a dropping funnel, freshly distilled phosphorus oxychloride (15 ml) was dropped into the reaction flask during about 30 minutes. The cooling bath was removed and the reaction mixture was then stirred for 30 minutes at room temperature. The mixture was cooled in an ice-bath and a solution of the compound **8** (26 g, 0.12 moles) in DMF (40 ml) was dropped into the reaction flask during a ¾ hour period so that the temperature of the reaction mixture was maintained in the range 8-10°. Then the mixture was warmed in a water bath for 2 hours at 37-38°. The opalescent yellow-red coloured solution obtained was poured over 150 g of crushed ice. The solution was neutralized (*p*H 8) under stirring by careful addition of a solution of sodium hydroxide (187 g) in water (500 ml) and then just warmed to boiling and finally cooled for 10 hours in a refrigerator. The crystallized product was collected by filtration and thoroughly washed, first with cold water (5 × 100 ml) and then with warm water (5 × 100 ml). About 25 g (85%) of pure (yellow) product was obtained, mp 111-112° (ethanol); ir: 1730, 1660; $^1$H-nmr (DMSO-$d_6$): 1.20 (t, C-$CH_3$, 3H), 3.75 (s, N-$CH_3$, 3H), 4.18 (q, O-$CH_2$, 2H), 4.45 (s, $CH_2$, 2H), 7.2-7.68 (m, $H_{5,6,7}$, 3H), 7.9-8.1 (m, $H_4$, 1H), 10.20 (s, CHO, 1H).

*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.

2-(1-Methylindole)acetohydrazide (**10**).

Compound **8** (4.3 g, 20 mmoles), in ethanol (50 ml) and 40% hydrazine hydrate (50 ml) was refluxed for 2 hours. The reaction mixture was cooled. Hydrazine and ethanol were removed *in vacuo*. The white residual material was collected by filtration and crystallized from ethanol to give **10** (3.25 g, 80%) as white needles, mp 126-128°; ir: 3300, 1650; $^1$H-nmr (DMSO-$d_6$): 3.68 (s, N-$CH_3$, 3H), 4.21 (s, $CH_2$, 2H), 6.25 (s, $NH_2$, 2H), 6.9-7.2 (m, $H_{5,6,7}$, 3H), 7.1-7.5 (m, $H_{3,4}$, 2H), 9.15-9.35 (bs, NH, 1H).

*Anal.* Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.31; H, 6.37; N, 20.60.

4-Hydroxy-3*H*[1,2]diazepino[5,6-*b*]indole (**11**).

Method A.

To a solution of **9** (1 g, 4 mmoles) in ethanol (50 ml), 90% hydrazine hydrate (15 g) was added. The yellow mixture was boiled for 1 hour. On cooling, white yellow needles crystallized. The material was collected by filtration, washed with water (5 × 100), and crystallized from 2-propanol to give **11** (0.78 g, 90%) of yellow-white needles, with mp 167-168°.

Method B.

Compound **11** was obtained from **10** by reaction with phosphorus oxychloride and *N,N*-dimethylformamide, in a similar manner to that described above, yield 90%; ir: 3280, 1660, 1610; $^1$H-nmr (DMSO-$d_6$): 3.60 (s, N-$CH_3$, 3H), 6.20-6.80 (bs, OH and NH, 2H), 6.25 (s, $H_5$, 1H), 7.1-7.55 (m, $H_{7,8,9}$, 3H), 7.95-8.10 (m, $H_{10}$, 1H), 8.7 (s, $H_1$, 1H).

*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, 19.61.

Ethyl 2-(3-*N,N*-Diethylaminomethylindole)carboxylate (**13**).

To a solution at 5° of acetic acid (20 ml, 60%) and diethylamine (7.3 g, 0.1 mole), formalin (5 ml, 37%) was added. After stirring for 1 hour at 5°, this solution was added under stirring to a cooled solution (5°) of **12** (5 g, 50 mmoles) in dioxane (20 ml). The resulting solution was heated to 64° and kept at this temperature for 4 hours. The mixture was then poured into cold sodium hydroxide (200 ml, 1*N*) and extracted with ether (3 × 250 ml). The extracts were washed with saturated sodium chloride solution. After drying over anhydrous sodium sulfate, ether was evaporated and the residue crystallized from ligroin as white crystals of **13** (6.2 g, 90%), mp 114-115°; ir: 3320, 1680; $^1$H-nmr (carbon tetrachloride): 1.1 (t, N-C-$CH_3$, 6H), 1.45 (t, O-C-$CH_3$), 2.55 (q, N-$CH_2$, 4H), 4.1 (s, C-$CH_2$-N, 2H), 4.45 (q, O-$CH_2$, 2H), 6.95-7.4 (m, $H_{3,6,7}$, 3H), 7.95-8.05 (m, $H_4$, 1H), 8.6-8.9 (bs, NH, 1H).

*Anal.* Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.84; H, 8.28; N, 9.82.

3-(2-Ethoxycarbonylindole)acetonitrile (**14**).

To a solution of **13** (1.4 g, 5 mmoles) and sodium cyanide (1.22 g, 25 mmoles) in ethanol/water/*N,N*-dimethylformamide (50 ml/50 ml/50 ml), methyl iodide (3.55 g, 20 mmoles) was added dropwise, over 1 hour. Stirring was continued for 72 hours at 25° and finally water at 5° (100 ml) was added. The solution was extracted with chloroform. The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the viscous oil residue crystallized from 2-propanol to give white-green crystals of **14** (0.5 g, 40%), mp 115-116°; ir: 3320, 1670; $^1$H-nmr (deuteriochloroform): 1.4 (t, $CH_3$, 3H), 4.21 (s, $CH_2$, 2H), 4.45 (q, O-$CH_2$, 2H), 7.1-7.5 (m, $H_{5,6,7}$, 3H), 7.7-7.85 (m, $H_4$, 1H), 9.1-9.4 (bs, 1H, NH).

*Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.70; H, 5.70; N, 12.42.

4,5-Dihydro-2-hydrazino-5-oxo-3*H*[1,2]diazepino[4,5-*b*]indole (**16**).

A mixture of compound **14** (2.28 g, 10 mmoles), 80% hydrazine hydrate (50 ml) and ethanol (50 ml) was boiled until the tlc showed that all of compound **14** had reacted (about 6 hours). Upon cooling the reaction mixture, white crystals of **15** (1.6 g, 70%) were obtained, mp 204° dec; ir: 3200-3370, 1660, 1630, 1600; $^1$H-nmr (DMSO-$d_6$): 3.3-4.6 (bs, 2NH, 2H), 5.7 (s, $NH_2$, 2H), 6.52 (s, CH, 1H), 7.05 (s, CONH, 1H), 6.95-7.7 (m, $H_{7,8,9}$, 3H), 7.95 (d, $H_{10}$, 1H), 11.2-11.6 (bs, $N_6$-H, 1H).

*Anal.* Calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.44; H, 4.78; N, 30.11.

Acknowledgement.

This work was supported by the "Comisión Asesora de Investigación Científica y Técnica" of Spain (contract No. 1433/1982).

## REFERENCES AND NOTES

[1] S. Garattini, E. Mussini and L. O. Randall, "The Benzodiazepines", Raven Press, New York, NY, 1973; L. O. Randall, W. Schallek, L. H. Sternbach and R. Y. Ning, "Chemistry and Pharmacology of the 1,4-Benzodiazepines", in Psychopharmacologic Agents, M. Gordon Ed, Academic Press, New York, Vol III, 1974, pp 175-287; L. H. Stembach, L. O. Randall and S. R. Gustafson, "1,4-Benzodiazepines (Chlordiazepoxide and Related Compounds)", in Psychopharmacologic Agents, M. Gordon, ed, Academic Press, New York, Vol I, 1964, pp 137-224.

[2] L. Fontanella, L. Mariani, G. Tarzia and N. Corsio, *Eur. J. Med. Chem.*, **11**, 217 (1976); D. Harris, S. Syren and J. Streith, *Tetrahedron Letters*, 4093 (1987).

[3] K. Grobe and H. Heitzer, *Ann. Chem.*, 1974 (1977); J. B. Press, C. M. Hofmann, N. H. Eudy, I. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem.*, **24**, 154 (1987).

[4] A. Edenhofer, *Helv. Chim. Acta*, **58**, 2192 (1975); J. R. Frost and Sheith, *J. Chem. Soc., Perkin Trans. I*, 1297 (1978).

[5] H. A. De Wald, S. Lobbestael and D. E. Butler, *J. Med. Chem.*, **20**, 1562 (1977).

[6] R. Jaunin, *Helv. Chim. Acta*, **57**, 1934 (1974).

[7] A. Surana, R. P. Tyagi and B. C. Joshi, *Philipp. J. Sci.*, **101**, 49 (1972); *Chem. Abstr.*, **82**, 170850 (1975).

[8] T. Tsnchiya and H. Sawanishi, Japan Patent 179-41887 (1979); *Chem. Abstr.*, **91**, 91680 (1979).

[9] Sh. Hendi and L. D. Basanagondar, *Indian J. Chem.*, **20B**, 288 (1981); S. Narute and O. Yonemitsu, *Chem. Pharm. Bull.*, **28**, 900 (1980); see also reference [13].

[10] M. Machida, H. Takechi and Y. Kawaoka, *Heterocycles*, **14**, 1255 (1980); *ibid.*, (Special issue), **7**, 273 (1977); see also reference [13].

[11] D. H. Kim, *J. Heterocyclic Chem.*, **13**, 1187 (1976); D. H. Kim and T. Baum, *J. Med. Chem.*, **20**, 209 (1977); H. P. Haerter, O. Strauss, J. H.

Osiecki and O. Schindler, *Chimia*, **30**, 50 (1976); L. Toscano, E. Seghetti and G. Fioriello, *J. Heterocyclic Chem.*, **13**, 475 (1976); F. Gatta and S. Chiavarelli, *Farmaco, Ed. Sci.*, **30**, 631 (1975); M. K. Eberle, G. G. Kahle and S. M. Talati, *Tetrahedron*, **29**, 4045 (1973).

[12] W. Nastasi, *Heterocycles*, **4**, 1509 (1976).

[13] A. Monge, M. T. Martínez, J. A. Palop, J. M. Mateo and E. Fernández-Alvarez, *J. Heterocyclic Chem.*, **18**, 889 (1981).

[14] M. C. Beltran, R. Madroñero and S. Vega, XVIII Reunión Bienal de la Real Sociedad Española de Física y Química, Común. 24.16 (síntesis orgánica), Sept. 29-Oct. 3, 1980, Burgos, Spain.

[15] A summary of this paper has been accepted for the Ninth International Congress of Heterocyclic Chemistry to be held in Tokyo on August 21-26, 1983.

[16] F. A. Trofimor, V. I. Ryabohenko and A. N. Griner, *Chem. Heterocyclic Compounds*, **10**, 1147 (1975).

[17] G. A. Bahadur, A. S. Bailey, N. W. Middleton and J. M. Peach, *J. Chem. Soc., Perkin Trans. I*, 1688 (1980).