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Studies on Tertiary Amine Oxides. LXXIX.[1] Reactions of 2-Ethoxycarbonyl-1-hydroxyindole in the Presence of Acylating Agents

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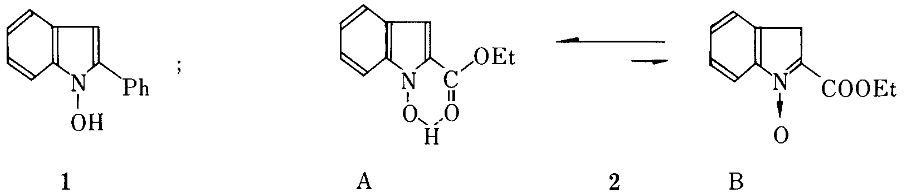
The Vilsmeier–Haack reaction of 2-ethoxycarbonyl-1-hydroxyindole (**2**) did not give 3-formylindoles but gave 3-chloro-2-ethoxycarbonylindole (**3**). The electrophilic reaction of **2** with quinoline 1-oxide (**4**) in the presence of benzoyl chloride or tosyl chloride also failed, 1-benzoyloxy-2-ethoxycarbonylindole (**6**) or **3** being formed, respectively.

The reaction of **2** with tosyl chloride, benzoyl chloride or acetic anhydride gave the corresponding 3-acyloxy-2-ethoxycarbonylindoles (**7**, **8** and **11**) in unsatisfactory yields. Treatment of **2** with tosyl chloride and 1-morpholinocyclohexene in pyridine–dimethylformamide afforded 2-ethoxycarbonyl-3-(2-oxocyclohexyl)indole (**13**) after hydrolysis of the reaction mixture.

Keywords——enehydroxylamine; nucleophilic reaction; 3-chloro-2-ethoxycarbonylindole; 3-acyloxy-2-ethoxycarbonylindole; 2-ethoxycarbonyl-3-(2-oxocyclohexyl)indole; quinoline 1-oxide; 1-morpholinocyclohexene

We previously reported that 1-hydroxy-2-phenylindole (**1**) is able to react with both electrophiles and nucleophiles in the presence of an acylating agent.[3] As an extension of this work, reactions of 2-ethoxycarbonyl-1-hydroxyindole (**2**)[4,5] with some electrophiles and nucleophiles were investigated under similar conditions.

In contrast to **1**, **2** may exist exclusively as the enehydroxylamine form (A) in usual organic solvents, the nitrone form (B) being negligible, on the basis of nuclear magnetic resonance (NMR) spectral examination; the C_3-methine signal of form A appears at δ 6.89—7.04, but no signal due to the C_3-methylene of form B is observed at all.[6] Apparently, intramolecular hydrogen bonding is responsible for this fixed configuration (Chart 1).



1 A 2 B

Chart 1

In order to explore the electrophilic reactivity of **2**, the Vilsmeier–Haack reaction and the reaction with quinoline 1-oxide in the presence of an acylating agent were tried.

A solution of **2** and phosphoryl chloride (1.1 eq) in dimethylformamide (DMF) was stirred at room temperature for 45 min to give 3-chloro-2-ethoxycarbonylindole[4] (**3**) in 50.5% yeild, no formation of 3-formylindoles being detected. The structure of the product was assigned on the basis of infrared (IR), NMR and mass (MS) spectral examinations, and confirmed by direct comparison with an authentic sample prepared from 3-ethoxycarbonylindole and phosphorus pentachloride.[4]

While reactions of **1** with quinoline 1-oxide (**4**) in the presence of benzoyl or tosyl chloride afforded 2-phenyl-3-(2-quinolyl)indoles (**5**), 2-ethoxycarbonyl-3-(2-quinolyl)indole derivatives were not formed in similar reactions of **2** with **4**. Thus, treatment of **2** with **4** in the presence of 3 mol of benzoyl chloride in boiling chloroform resulted only in the formation of 1-benzoyloxy-2-ethoxycarbonylindole[4] (**6**) in 66% yield. An attempted reaction of **2** with **4** in DMF using tosyl chloride in place of benzoyl chloride at around −20 °C also gave not 3-(2-quinolyl)indoles but the 3-chloroindole (**3**) as the sole product in 43% yield (Chart 2).

Thus, attempted electrophilic reactions of **2** failed, and **3** was formed by nucleophilic reaction. These results may be due to the electron-attracting character of the 2-ethoxycarbonyl substituent.

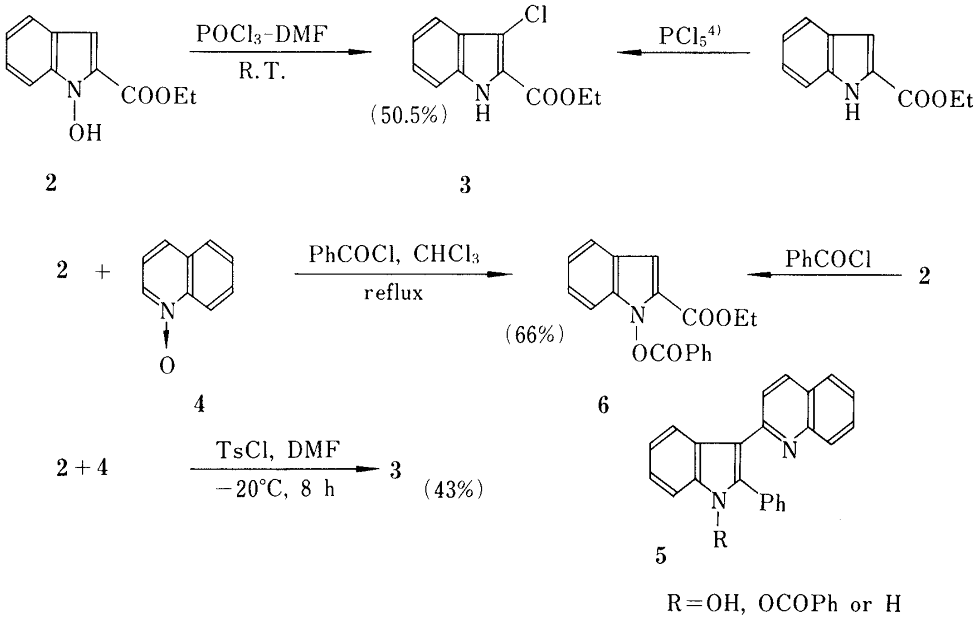


Chart 2

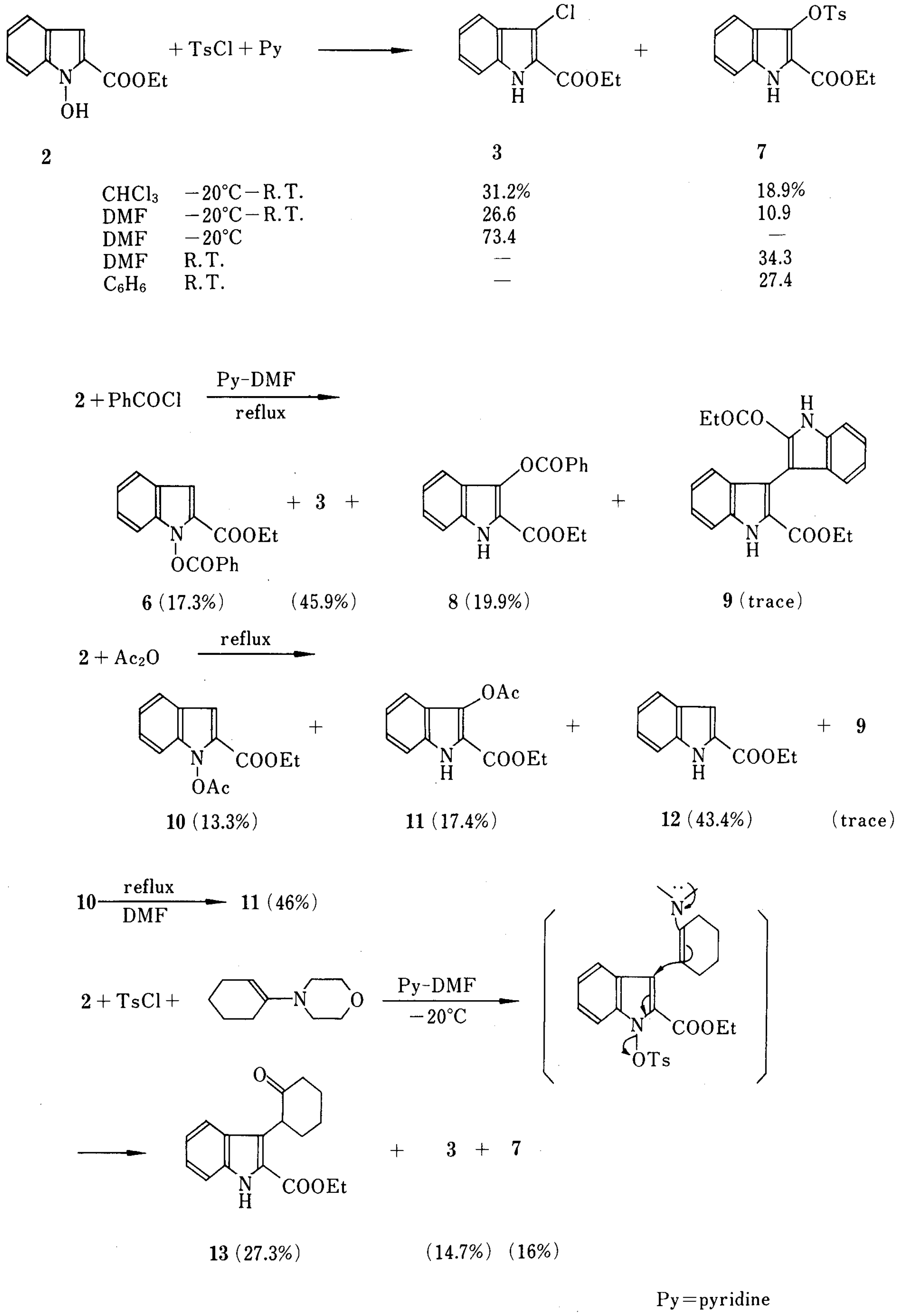
The reactivity of **2** towards nucleophiles was subsequently examined. Gabriel *et al.*[4] reported that **2** undergoes O-alkylation or O-benzoylation upon treatment with alkyl chlorides or benzoyl chloride in the presence of sodium methoxide, and gives the O-acetyl derivatives on heating with acetic anhydride. While **1** reacts with acylating agents, such as tosyl chloride, benzoyl chloride and acetic anhydride, to give the corresponding 3-acyloxy-2-phenylindoles *via* 1-acyloxyindoles,[3b,7] no comparable reactions have been reported for **2**. We therefore investigated reactions of **2** with tosyl chloride, benzoyl chloride and acetic anhydride taking into account the results obtained with **1**.

A solution of **2**, tosyl chloride (1.4 eq) and pyridine in chloroform was stirred at around −20 °C for 6 h and then at room temperature for one day to give **3** and 2-ethoxycarbonyl-3-tosyloxyindole (**7**) in 31.2 and 18.9% yields, respectively. A similar reaction using DMF as the solvent also afforded **3** and **7** in 26.6 and 10.9% yields, respectively. It was further found that the reaction at around −20 °C gave only **3** in a good yield of 73.4%, whereas that at room temperature gave only **7** in 34.3% yield. The reaction in benzene at room temperature also gave **7** as the sole product. The formation of **7** seems to be enhanced with increasing temperature, but optimization of the reaction was not done (Chart 3).

When a DMF solution of **2**, benzoyl chloride (1.5 eq) and pyridine was refluxed for 5 h, the 3-chloroindole **3** (45.9%), the 1-benzoyloxyindole **6** (17.3%), 3-benzoyloxy-2-

ethoxycarbonylindole (**8**) (19.9%) and a trace of 2,2′-diethoxycarbonyl-3,3′-bisindole[4] (**9**) were obtained (Chart 3).

Vigorous refluxing of **2** with acetic anhydride for 3 h afforded 3-acetoxy-2-ethoxycarbonylindole (**11**) in 17.4% yield together with 1-acetoxy-2-ethoxycarbonylindole[4] (**10**) (13.3%) and **9** (trace), but the major product was the deoxygenation product, 2-ethoxycarbonylindole[4] (**12**) (43.4%). Nevertheless, when a solution of **10** in DMF was vigorously refluxed for 5 h, **11** was isolated in a fair yield of 46%, neither **12** nor **9** being



		3	7
$CHCl_3$	−20°C−R.T.	31.2%	18.9%
DMF	−20°C−R.T.	26.6	10.9
DMF	−20°C	73.4	—
DMF	R.T.	—	34.3
C_6H_6	R.T.	—	27.4

Chart 3

detected in this case. As in the case of **1** fairly strong conditions were required for the formation of **11**; heating of **2** with acetic anhydride on a boiling water-bath, for instance, gave only **10**, neither **11** nor **12** being detected (Chart 3).

Finally, the reaction with nucleophilic carbon compounds was explored. Tosyl chloride (1.4 eq) was added to an ice-salt-cooled solution of **2** and pyridine in DMF. After 30 min, 3.5 eq of 1-morpholinocyclohexene was added, and the reactants were stirred under ice-salt cooling for 6 h. After treatment of the reaction mixture with 10% hydrochloric acid, the products were subjected to chromatography on silica gel to give 2-ethoxycarbonyl-3-(2-oxocyclohexyl)indole (**13**) in 27.3% yield together with **3** (14.7%) and **7** (16%). This result is comparable to that obtained in the similar reaction of **1**[3b)] (Chart 3).

The reaction of **2** with active methylene compounds did not give satisfactory results. However, in the reaction with ethyl acetoacetate and tosyl chloride in pyridine–DMF, a product, assumed to be ethyl α-(2-ethoxycarbonyl-3-indolyl)acetoacetate from its NMR spectrum, was obtained in a minute amount in addition to **3** (18.4%) and **7** (28.6%) (Chart 3).

Though the results were not so satisfactory, nucleophilic reactions of **2** were found to proceed in the same way as in the case of **1**; the formation of **13** from the reaction with 1-morpholinocyclohexene may be considered to be particularly significant. It should be pointed out that there is a marked tendency for **3** to be formed in reactions in the presence of an acyl chloride, and this seems to be a characteristic of the reactivity of **2**.

Experimental[8)]

Reaction of 2-Ethoxycarbonyl-1-hydroxyindole (2) with $POCl_3$–DMF——To a solution of $POCl_3$ (0.5 ml, 1.1 eq) in DMF (5 ml) previously prepared under ice-cooling and stirring, **2** (1 g) was added. The mixture was stirred at room temperature for 45 min, then 10% NaOH (5 ml) was added. The whole was poured into a large amount of H_2O (*ca.* 25 ml). The resulting precipitate was collected and recrystallized from *n*-hexane to give 0.55 g (50.5%) of 3-chloro-2-ethoxycarbonylindole (**3**), colorless needles, mp 154—156 °C [lit.[4)] mp 153—154 °C]. MS *m/e*: 224 (M^+), 226 ($M^+ + 2$). IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1690 (C=O). NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 4.48 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.10—7.78 (4H, m, Ar-H), 9.30 (1H, br s, NH).

Reaction of 2 with Quinoline 1-Oxide (4)——1) PhCOCl (2 g, 3 eq) was added to a solution of **2** (1 g) and **4** (0.8 g, 1.1 eq) in $CHCl_3$ (20 ml) and the whole was refluxed for 4 h. The reactants were stirred for 1 h with a saturated $NaHCO_3$ solution (10 ml), then concentrated under reduced pressure, and the residue was chromatographed on silica gel with *n*-hexane–benzene (1 : 1) to give 1.03 g (68.2%) of 1-benzoyloxy-2-ethoxycarbonylindole (**6**), pale yellowish scales, mp 104—105 °C (EtOH) [lit.[4)] mp 104—105 °C].

2) TsCl (1.5 g) was added to an ice-salt-cooled solution of **2** (1 g) in DMF (10 ml). After 30 min, **4** (0.85 g, 1.2 eq) was added and the whole was stirred for 8 h at the same temperature. The reactants were stirred with a saturated $NaHCO_3$ solution (10 ml) for 1 h, and then extracted with CH_2Cl_2 to give 0.4 g (43%) of **3**.

Reaction of 2 with TsCl——1) To an ice-salt-cooled solution of **2** (1 g) and pyridine (3 ml) in $CHCl_3$ (15 ml), TsCl (1.5 g, 1.4 eq) was added, and the whole was stirred at the same temperature for 6 h then at room temperature for 1 d. The reaction mixture was stirred with a saturated $NaHCO_3$ solution for 1 h and concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give successively 0.34 g (31.2%) of **3** and 0.33 g (18.9%) of 2-ethoxycarbonyl-3-tosyloxyindole (**7**), colorless needles, mp 153—154 °C (*n*-hexane–CH_2Cl_2). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.17; H, 4.74; N, 3.90. Found: C, 60.32; H, 4.48; N, 4.06. MS *m/e*: 359 (M^+), 314 ($M^+ - OCH_2CH_3$). IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1690 (C=O), 1385 (SO_2), 1270 (C–O–CO), 1195 (SO_2). NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.45 (3H, s, CH_3), 4.30 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 7.18—7.80 (8H, m, Ar-H), 9.20 (1H, br s, NH).

2) A solution of **2** (0.5 g), TsCl (0.75 g, 1.4 eq) and pyridine (2 ml) in DMF (10 ml) was processed in a similar way to give 0.14 g (26.6%) of **3** and 0.095 g (10.9%) of **7**.

3) A solution of **2** (0.5 g), TsCl (0.75 g, 1.4 eq) and pyridine (2 ml) in DMF (10 ml) was stirred at around −20 °C for 6 h to give 0.4 g (73.4%) of **3**.

4) A solution of **2** (0.5 g), TsCl (0.75 g, 1.4 eq) and pyridine (2 ml) in DMF (10 ml) was stirred at room temperature for 1 d to give 0.3 g (34.3%) of **7**.

5) A solution of **2** (1 g), TsCl (1.5 g, 1.4 eq) and pyridine (3 ml) in benzene (20 ml) was stirred at room temperature for 1 d to give 0.48 g (37.4%) of **7**.

Reaction of 2 with PhCOCl——A solution of **2** (1 g), PhCOCl (1 g, 1.5 eq) and pyridine (3 ml) in DMF (10 ml) was refluxed for 5 h. The reaction mixture was stirred with H_2O (20 ml) for 1 h and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. Elution with *n*-hexane–benzene (1 : 1) gave successively 0.26 g (17.3%) of **6** and 0.5 g (45.9%) of **3**. The next fraction, eluted with benzene, gave 0.3 g (19.9%) of 3-benzoyloxy-2-ethoxycarbonylindole (**8**), colorless needles, mp 154—156 °C (*n*-hexane–CH_2Cl_2). *Anal.* Calcd for $C_{18}H_{15}NO_4$: C, 69.90; H, 4.85; N, 4.53. Found: C, 69.67; H, 4.97; N, 4.39. MS *m/e*: 309 (M^+), 264 ($M^+ - OCH_2CH_3$), 204 (M^+ −COPh). IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1748, 1685 (C=O). NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 4.30 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.23—8.40 (9H, m, Ar-H), 9.10 (1H, br s, NH). Further elution with CH_2Cl_2 gave a trace of 2,2′-diethoxycarbonyl-3,3′-bisindole[4] (**9**) which was characterized by MS.

Reaction of 2 with Ac_2O——A solution of **2** (1 g) in Ac_2O (10 ml) was vigorously refluxed for 3 h and then concentrated under reduced pressure. The residue was chromatographed on silica gel. The eluate with *n*-hexane–benzene (2 : 1) gave 0.4 g (43.7%) of 2-ethoxycarbonylindole (**12**), colorless needles, mp 125—126 °C (EtOH) [lit.[4] mp 125—126 °C], and that with *n*-hexane–benzene (1 : 1) gave 0.16 g (13.3%) of 1-acetoxy-2-ethoxycarbonylindole (**10**), colorless needles, mp 76—77 °C (EtOH) [lit.[4] mp 76—77 °C]. The fraction eluted with benzene gave 0.21 g (17.4%) of 3-acetoxy-2-ethoxycarbonylindole (**11**), colorless needles, mp 98—100 °C (*n*-hexane–benzene). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.16; H, 5.26; N, 5.67. Found: C, 63.35; H, 5.03; N, 5.52. MS *m/e*: 247 (M^+), 204 ($M^+ - COCH_3$), 188 ($M^+ - OCOCH_3$). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1765, 1695 (C=O). NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.60 (3H, s, $COCH_3$), 4.43 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.20—7.76 (4H, m, Ar-H), 9.10 (1H, s, NH). Further elution with CH_2Cl_2 gave a trace of **9**.

Conversion of 10 to 11——A solution of **10** (0.5 g) in DMF (10 ml) was refluxed for 5 h and the products were chromatographed on silica gel with benzene to give 0.23 g (46%) of **11**.

Reaction of 2 with 1-Morpholinocyclohexene——TsCl (1.5 g, 1.4 eq) was added to an ice-salt-cooled solution of **2** (1 g) and pyridine (3 ml) in DMF (15 ml). After 30 min, 1-morpholinocyclohexene (3 g, 3.5 eq) was added to the solution and the whole was stirred at the same temperature for 6 h. The reaction mixture was stirred with 10% HCl (20 ml) at room temperature for 2 h, and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. Elution with *n*-hexane–benzene (1 : 1) gave successively 0.16 g (14.7%) of **3** and 0.28 g (16%) of **7**. The next fraction, eluted with benzene, gave 0.38 g (27.3%) of 2-ethoxycarbonyl-3-(2-oxocyclohexyl)indole (**13**), pale yellow needles, mp 141—143 °C (*n*-hexane–CH_2Cl_2). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.58; H, 6.67; N, 4.91. Found: C, 71.48; H, 6.48; N, 4.80. MS *m/e*: 285 (M^+), 256 ($M^+ - C_2H_5$), 240 ($M^+ - OCH_2CH_3$), 212 ($M^+ - COOC_2H_5$). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1715, 1680 (C=O). NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 1.2—3 (8H, m, 2-oxocyclohexyl C_3–C_6–H), 4.3 (1H, t, 2-oxocyclohexyl C_1–H), 4.33 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.2—7.7 (4H, m, Ar-H), 9.2 (1H, br s, NH).

References and Notes

1) Part LXXVIII: S. Saeki, T. Hayashi, and M. Hamana, *Heterocycles*, **22**, 545 (1984).
2) Present address: *Central Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada 3–41–8, Toshima-ku, Tokyo 171, Japan.*
3) *a*) T. Nagayoshi, S. Saeki, and M. Hamana, *Chem. Pharm. Bull.*, **29**, 1827 (1981); *b*) *Idem, ibid.*, **29**, 1920 (1981).
4) S. Gabriel, W. Gerhard, and R. Wolter, *Chem. Ber.*, **56**, 1024 (1923).
5) I. Baxter and G. A. Swan, *J. Chem. Soc.*, (*C*), **1967**, 2446.
6) The β-H resonance signal of **2** (solvent): 6.89 (CCl_4); 7.00 ($CDCl_3$); 7.04 (CD_3OD); 7.04 (DMF); 7.04 (DMSO).
7) R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965).
8) All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL JNM-C60H at 60 MHz or a JEOL JNM-PS-100 MHz using TMS as an internal reference. MS were obtained on a JMS 01SG spectrometer.