solution was worked up as described above (see b) in the preceding section). The orange oil obtained (357 mg) consisted mainly of the acetoxylated Schiff base (VIIb). IR $\nu_{\text{max}}^{\text{NaCl}}$ cm^{-1} : 2950, 1770, 1633, 1475, 1275, 1200. PMR (CDCl_3) δ :¹²⁾ 1.35 (9H, singlet, $\text{C}(\text{CH}_3)_2$), 2.04 (3H, singlet, COCH_3), 2.32 (3H, singlet, Ar-CH_3), 3.82 (3H, singlet, Ar-OCH_3), 6.62 (1H, singlet, ArH), 8.19 (1H, singlet, Ar-CH=N-); the signal for the proton of the hydroxyl group was not discernible.

The product obtained above (250.5 mg) was subjected to controlled potential electrolysis at 0.75 V until the value of the current fell below 1% of the initial value. From the current-time curve 144 C, which corresponded to $n=1.7$, was found to have been consumed. Work-up of the anolyte as described above (see a) in the preceding section) gave IIIb in 72% yield (142.7 mg).

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Facile Preparation of 5-(3-Indolylmethylene)hydantoins

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A facile preparation of 5-(3-indolylmethylene)hydantoins, which are useful intermediates for syntheses of tryptophan and its derivatives, was achieved by condensation of hydantoin with 3-(aminomethylene)-3H-indoles formed *in situ* by the reaction of indoles with Vilsmeier-Haack reagent followed by neutralization with anhydrous bases.

Keywords—tryptophan; hydantoin; 5-(3-indolylmethylene)hydantoin; 3-(aminomethylene)-3H-indole; Vilsmeier-Haack reaction; condensation

It is desirable to develop a convenient synthetic method for tryptophan, an essential amino acid, and its derivatives, some of which are of interest as nonnutritive sweeteners²⁾ or are components of interesting bioactive peptides.³⁾ The synthesis of 5-(3-indolylmethylene)-hydantoin (**5a**) which is a useful intermediate for the preparation of tryptophan,⁴⁾ has been conventionally performed through two steps *via* indolecarbaldehyde (**4a**): the formylation of indole (**1a**) and subsequent condensation with hydantoin in a secondary amine (route A in the Chart).^{4a,5)} In the preceding paper, we reported⁶⁾ that 3-(aminomethylene)-3H-indole (**3**) is reactive towards active methylene compounds, affording condensation products in good yields. Concerning **3**, Smith reported⁷⁾ that 3-(dimethylaminomethylene)-3H-indole was formed as an unstable intermediate in the synthesis of **4a** by neutralization of the iminium salt (**2**) which was generated by the reaction of **1a** with Vilsmeier-Haack reagent. These results suggest that Smith's intermediate (**3**) might be available for the preparation of

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Chart

Knoevenagel condensation products of **4a** by condensation with active methylene compounds. In this paper, we report a facile preparation of 5-(3-indolylmethylene)hydantoins (**5**) utilizing the intact intermediate (**3**) for condensation with hydantoin (route B in the Chart).

The 3-(aminomethylene)-3H-indole (**3**) was formed *in situ* by the reaction of **1** with various Vilsmeier-Haack reagents followed by neutralization with anhydrous bases. At this stage, the formation of **3** was confirmed by the presence of an absorption band at 354 nm^{6,7)} in the UV spectrum of the ethereal extract from the reaction mixture. Subsequently, without isolation or purification of **3**, condensation with hydantoin was carried out under the reaction conditions given in the Table to afford **5**. As shown in the Table, the complex of dimethylformamide (DMF) and phosphoryl chloride was convenient as a Vilsmeier-Haack reagent in this reaction, though various combinations of usually employed reagents were also suitable. When N-methylformanilide was used instead of DMF, however, only **4** was formed, probably because of the susceptibility of the intermediate to hydrolysis. Organic and inorganic bases could be used for the neutralization of **2**. However, the use of sodium hydroxide, which liberates much water upon neutralization, decreased the yield of **5** because of the increase in the hydrolysis of the intermediate (**3**). Among the reactions examined, the combination of DMF, phosphoryl chloride, and sodium carbonate gave the best result, affording **5a** in 98% yield. Some 5-(3-indolylmethylene)hydantoins (**5b-d**) were similarly obtained from the corresponding substituted indoles (**1b-d**).

TABLE. Preparation of 5-(3-Indolylmethylene)hydantoins (**5a-d**)

Compound No.	R	Vilsmeier-Haack reagent	Base	Solvent	Temp. (°C)	Time (hr)	Yield (%)
5a	H	DMF-POCl ₃	Na ₂ CO ₃	DMF	110	7	98
5a	H	DMF-COCl ₂	Na ₂ CO ₃	DMF	110	7	64
5a	H	DMF-TsCl	Na ₂ CO ₃	DMF	110	7	66
5a	H	DMF-PhCOCl	Na ₂ CO ₃	EtOH	80	7	20
5a	H	-NCHO-POCl ₃	Na ₂ CO ₃	EtOH	80	4	76
5a	H	-NCHO-POCl ₃	Na ₂ CO ₃	EtOH	80	4	59
5a	H	PhNCH ₃ CHO-POCl ₃	Na ₂ CO ₃	EtOH	80	7	0
5a	H	DMF-POCl ₃	NaOH	DMF	110	7	10
5a	H	DMF-POCl ₃	Et ₂ NH	DMF	100	4	91
5b	6-Cl	DMF-POCl ₃	Na ₂ CO ₃	DMF	110	7	53
5c	6-Me	DMF-POCl ₃	Na ₂ CO ₃	DMF	110	7	86
5d	5-MeO	DMF-POCl ₃	Na ₂ CO ₃	DMF	110	7	55

The major advantage of the new preparative method for **5** from **1** (route B) is that isolation of **4** is not necessary, while the dimethylamino group in DMF is effectively utilized to form the highly reactive **3**. Thus, the new method is convenient and economical in comparison with the conventional method (route A).

Experimental⁸⁾

Typical Procedure for the Preparation of 5a—Phosphoryl chloride (8.43 g, 55 mmol) was added dropwise to DMF (75 g) with stirring, keeping the temperature below 0°. A solution of **1a** (5.86 g, 50 mmol) in DMF (15 g) was then added slowly with stirring at the same temperature. After addition, the temperature was kept at 35° for 1 hr, then anhydrous sodium carbonate (20.5 g, 195 mmol) was added with stirring at 0°. Hydantoin (5.50 g, 55 mmol) was added to the resulting mixture and the temperature was gradually raised to 110° over a 2 hr period. After heating for 7 hr at the same temperature with stirring, the mixture was concentrated to dryness under reduced pressure. Hot water (150 ml) and 10% HCl (70 ml) were added to the residue. Filtration and washing with ethanol and water gave fine yellow crystals of **5a** (11.10 g, 98%); mp > 280°. The spectral data for **5a** were identical with those of an authentic sample.^{4a)}

In this way, various combinations of Vilsmeier-Haack reagents and bases were used for the preparation of **5a** from **1a**. The results are shown in the Table.

Substituted indoles (**1b–d**) were treated in a similar manner to afford the corresponding 5-(3-indolylmethylene)hydantoins (**5b–d**). The reaction conditions and yields are given in the Table.

5-(6-Chloro-3-indolylmethylene)hydantoin (5b)—Yellow prisms (DMF–EtOH), mp > 280°. *Anal.* Calcd for C₁₂H₈ClN₃O₂: C, 55.08; H, 3.08; Cl, 13.55; N, 16.06. Found: C, 55.34; H, 3.37; N, 16.25; Cl, 13.68. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3310, 3140, 3050, 1745, 1710, 1650, 1532, 1255. NMR (DMSO-*d*₆) δ : 6.77 (1H, s, olefinic H), 7.13 (1H, dd, *J* = 1.9 and 9.0 Hz, C-5H), 7.51 (1H, d, *J* = 1.9 Hz, C-7H), 7.82 (1H, d, *J* = 9.0 Hz, C-4H), 8.20 (1H, broad s, addition of D₂O sharpened this absorption, C-2H), 10.16, 11.05, and 11.90 (1H each, broad, D₂O-exchangeable, NH).

5-(6-Methyl-3-indolylmethylene)hydantoin (5c)—Yellow prisms (DMF–EtOH), mp > 280°. *Anal.* Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.59; N, 17.41. Found: C, 64.46; H, 4.83; N, 17.55. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3360, 3300, 3130, 1740, 1700, 1650, 1250. NMR (DMSO-*d*₆) δ : 2.43 (3H, s, CH₃), 6.76 (1H, s, olefinic H), 6.99 (1H, broad d, *J* = 8.3 Hz, C-5H), 7.25 (1H, broad s, C-7H), 7.70 (1H, d, *J* = 8.3 Hz, C-4H), 8.10 (1H, broad s, addition of D₂O sharpened this absorption, C-2H), 11 (3H, broad, D₂O-exchangeable, NH).

5-(5-Methoxy-3-indolylmethylene)hydantoin (5d)^{4d)}—Yellow prisms (DMF–EtOH), mp > 280°.

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8) All melting points are uncorrected. IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. ¹H-NMR spectra were recorded on a Hitachi R-20A instrument, using TMS as an internal standard.