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 ν_{max}^{Nujol} cm^{-1}: 2950, 1770, 1633, 1475, 1275, 1200. PMR ($CDCl_3$) δ:[12] 1.35 (9H, singlet, $C(CH_3)_2$), 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).

[Chem. Pharm. Bull. 28(6)1891—1893(1980)]

Facile Preparation of 5-(3-Indolylmethylene)hydantoins

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(Received November 19, 1979)

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 sweeteners[2] 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 reported[6] that 3-(aminomethylene)-3H-indole (**3**) is reactive towards active methylene compounds, affording condensation products in good yields. Concerning **3**, Smith reported[7] 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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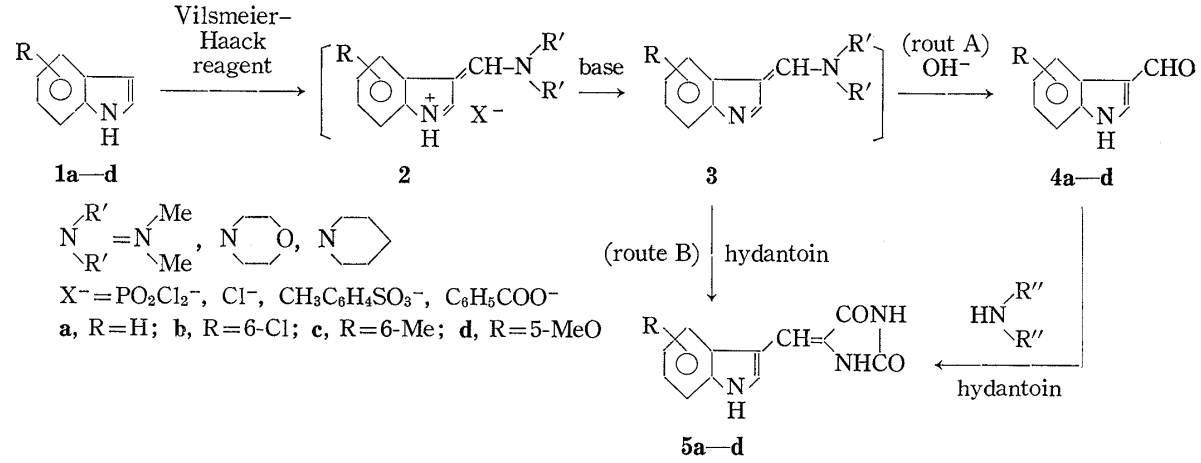
6) T. Moriya, K. Hagio, and N. Yoneda, *Chem. Pharm. Bull.*, **28**, 1711 (1980).
7) G.F. Smith, *J. Chem. Soc.*, **1954**, 3842.

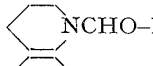
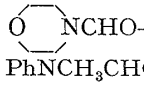


Chart

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 ususally 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_2CO_3	DMF	110	7	98
5a	H	DMF–$COCl_2$	Na_2CO_3	DMF	110	7	64
5a	H	DMF–TsCl	Na_2CO_3	DMF	110	7	66
5a	H	DMF–PhCOCl	Na_2CO_3	EtOH	80	7	20
5a	H		Na_2CO_3	EtOH	80	4	76
5a	H		Na_2CO_3	EtOH	80	4	59
5a	H	$PhNCH_3CHO$–$POCl_3$	Na_2CO_3	EtOH	80	7	0
5a	H	DMF–$POCl_3$	NaOH	DMF	110	7	10
5a	H	DMF–$POCl_3$	Et_2NH	DMF	100	4	91
5b	6-Cl	DMF–$POCl_3$	Na_2CO_3	DMF	110	7	53
5c	6-Me	DMF–$POCl_3$	Na_2CO_3	DMF	110	7	86
5d	5-MeO	DMF–$POCl_3$	Na_2CO_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).

Experimental[8)]

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 $C_{12}H_8ClN_3O_2$: 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 ν_{max}^{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 D_2O sharpened this absorption, C-2H), 10.16, 11.05, and 11.90 (1H each, broad, D_2O-exchangeable, NH).

5-(6-Methyl-3-indolylmethylene)hydantoin (5c)——Yellow prisms (DMF–EtOH), mp>280°. *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.59; N, 17.41. Found: C, 64.46; H, 4.83; N, 17.55. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3300, 3130, 1740, 1700, 1650, 1250. NMR (DMSO-d_6) δ: 2.43 (3H, s, CH_3), 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 D_2O sharpened this absorption, C-2H), 11 (3H, broad, D_2O-exchangeable, NH).

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

Acknowledgement We wish to express our thanks to Dr. Ichiro Chibata and Dr. Muneji Miyoshi for their encouragement throughout the present study.

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