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SYNTHESES OF 4-ALKYLINDOLES FROM 2-METHYL-5-NITROISOQUINOLINIUM IODIDE[1]

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4-[N-Acetyl-N-methyl]aminomethylindole was prepared economically on a large scale from 2-methyl-5-nitroisoquinolinium iodide. Subsequent alkaline hydrolysis afforded 4-methylaminomethylindole. Starting from these two compounds, various 3,4-di- and 4-substituted indoles were prepared including 4-formylindole, 4-[N,N-disubstituted]aminomethylindoles, 4-alkylindoles, and benz[cd]indoles. A novel nucleophilic substitution reaction of gramine derivatives by the catalysis of tri-n-butylphosphine was also reported.

In this paper, we report convenient and economical synthetic routes to various 4-substituted indoles, which can be carried out on a multigram scale.

I. The preparation of 4-[N-acetyl-N-methyl]aminomethylindole

In our previous communication,[2] a one-step synthesis of 4-methylaminomethylindole (II) from 2-methyl-5-nitroisoquinolinium iodide (I) by the action of aqueous $TiCl_3$ was reported. However, chromatographic separation of the crude products has hindered it from being used on a large scale.

We now have found that further treatment of the products with Ac_2O-pyridine affords 4-[N-acetyl-N-methyl]aminomethylindole (III, mp 154.5-155.5 °C) in 24% yield, simply by recrystallization from H_2O-MeOH. By this modification, the compound (III), a suitable starting material for the preparation of various 4-substituted indoles, is now readily available from I on a multigram scale.

II. The preparation of 4-[N,N-disubstituted]aminomethylindoles[3]

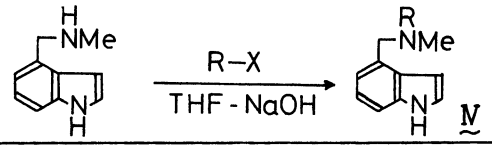
Hydrolysis of III with 30% aqueous NaOH-MeOH (2:1, v/v) by refluxing for 4 h under argon gave II in a quantitative yield. Further treatment of II with alkyl halide, such as methyl iodide, allyl, benzyl, and propargyl bromide, in two phases using THF-30% aqueous NaOH (1:1, v/v), led to the corresponding 4-[N,N-disubstituted]aminomethylindoles (IVa-d) in good yields. The results are summarized in Table I.

III. The preparation of 4-formylindole by three routes

1) Oxidation of II with 4 equivalents of $KMnO_4$ in aqueous acetone at 0 °C for 5 min produced 4-formylindole (V, mp 135-137 °C)[4] in 37% yield. This constitutes two-step synthesis of V from I.

2) 4-Dimethylaminomethylindole (IVa) was converted to a mixture of 4-acetoxymethylindole (VI) and 1-acetyl-4-acetoxymethylindole (VII) by the treatment with Ac_2O at reflux for 3.5 h. Subsequent hydrolysis of the mixture with 2N-NaOH in MeOH by refluxing for 1 min led to 4-hydroxymethylindole (VIII, mp 56-57.5 °C)[5] in

Table I. 4-[N,N-Disubstituted]indoles



	R-X	Yield, %
a)	MeI	66, mp 124-126 °C
b)	$HC{\equiv}C\text{-}CH_2Br$	55, mp 69-70 °C
c)	$H_2C{=}CH\text{-}CH_2Br$	65, oil
d)	$Ph\text{-}CH_2Br$	67, oil

83% overall yield. Oxidation of VIII with active MnO_2 in acetone afforded 4-formylindole (V) in 73% yield.

3) The compound (III) was reduced with $LiAlH_4$ in THF to give 4-[N-ethyl-N-methyl]aminomethylindole (IX, mp 58-59 °C) in a quantitative yield. Treatment of IX with refluxing Ac_2O and subsequent hydrolysis under the condition described in 2) led to 4-hydroxymethylindole (VIII) in 81% yield, via VI and VII.

The synthesis of V constitutes a formal synthesis of 4-dimethylallyltryptophan, since Plieninger et al. reported its total synthesis using V as the key intermediate.

IV. The preparation of benz[cd]indole derivatives

Aldol condensation of 4-formylindole (V) with acetone using 3.3% aqueous NaOH led to 4-[indol-4-yl]-3-buten-2-one (X, mp 126-127 °C) in 98% yield. The compound (X) was also prepared from II in 8% yield, together with 73% yield of recovery, by the oxidation with active MnO_2 in acetone in the presence of NaOH. Mannich reaction of X using dimethylamine and formaldehyde in AcOH afforded 4-[3-dimethylaminomethylindol-4-yl]-3-buten-2-one (XI, mp 165-167 °C) in 90% yield.

Subsequently, the reaction of XI with nitromethane in CH_3CN was investigated with NaOH, Na_2CO_3, KF, KF-crownether, Ph_3P, or $(n\text{-}Bu)_3P$ as a catalyst. While the former five reagents provided 5-acetonyl-1,3,4,5-tetrahydro-4-nitrobenz[cd]indole (XII) in poor yields, tri-n-butylphosphine[6] afforded XII in 77% yield.

The product (XII)[7] was a mixture of diastereoisomers (XIIt and XIIc in ca. 3:1 ratio) of which the major isomer (XIIt,[7a] mp 136-138 °C) was assigned to have trans configuration based on the following facts: 1) The proton coupling constant between H_4 and H_5 in XIIt was 6.5 Hz, while that of the minor isomer (XIIc,[7b] mp 136-138 °C) was 4 Hz; 2) treatment of the major isomer with n-BuLi in THF, followed by protonation with AcOH resulted in exclusive formation of the minor isomer; 3) the major isomer was converted to the acetal (XIII, oil) in 94% yield by the treatment with benzene-ethylene glycol-p-TsOH by refluxing for 6 h, whereas the minor isomer was recovered under the same reaction condition.

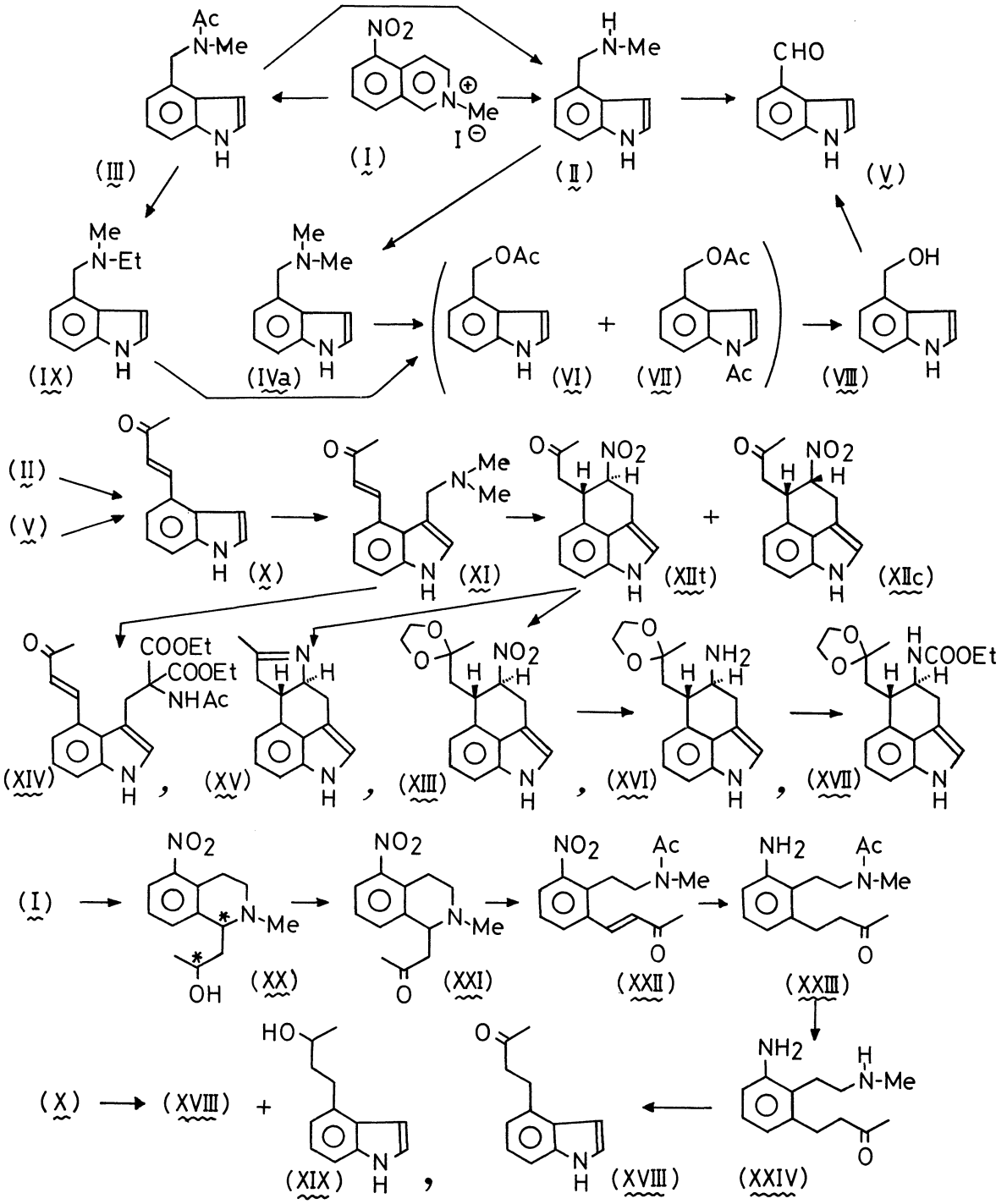
Tri-n-butylphosphine also catalyzed the reaction of XI with ethyl α-acetaminomalonate affording the compound (XIV, mp 173-175 °C) in 72% yield. In addition, the gramine derivatives were found to undergo nucleophilic substitution reaction by the catalysis of the reagent.[8] Further extention to the related Mannich bases are currently in progress.

The major isomer (XIIt) was led to the imine (XV, mp 216-218 °C) in 94% yield by the reaction with zinc-HCl. On the other hand, hydrogenation of the acetal

(XIII) with 5% Pd-C at 60 °C and 100 kg/cm^2 afforded the corresponding amine (XVI, oil) in 78% yield. Further reaction of XVI with ethyl chloroformate-NEt_3 in CH_2Cl_2 provided the ethyl carbamate[9] (XVII, mp 132-133 °C) in 95% yield. Synthesis of Ergot alkaloids utilizing these products (X-XVII) is in progress.

V. The preparation of 4-[indol-4-yl]butan-2-one by two routes

1) Hydrogenation of X over 5% Pd-C in MeOH gave 4-[indol-4-yl]butan-2-one (XVIII, mp 50-53 °C) and the corresponding alcohol (XIX, oil) in 64% and 30%



yields, respectively.

2) 1,2,3,4-Tetrahydro-1-[2-hydroxypropyl]-2-methyl-5-nitroisoquinoline (XX, a mixture of diastereoisomers) was synthesized from I by the previous procedure.[10] Jones oxidation of XX afforded 1-acetonyl-1,2,3,4-tetrahydro-2-methyl-5-nitroisoquinoline (XXI, oil) in 91% yield. Refluxing of XXI in Ac_2O caused ring opening and the desired compound (XXII, mp 114-115 °C) was obtained in 91% yield. The geometry of the newly formed double bond was assigned to be trans based on the proton coupling constant (J=17 Hz). Hydrogenation of XXII over 5% Pd-C resulted in the reduction of both the nitro group and double bond, affording the compound (XXIII, mp 125-126 °C) in 63% yield, together with the corresponding alcohol derivative in 23% yield. Subsequent hydrolysis of XXIII with 6N-HCl in MeOH gave the compound (XXIV, oil) in 77% yield. Finally, oxidation of XXIV with active MnO_2 in CH_2Cl_2 gave XVIII in 20% yield.

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References and Notes

All new compounds gave satisfactory elemental analysis and spectral data.

1) Presented partly at the 99th Meeting of the Pharmaceutical Society of Japan, Abstracts Papers, p. 276 (1979); 12th Congress of Heterocyclic Chemistry (Japan), Tokyo, 1979. Abstracts Papers, p. 91. This paper is part XI of a series entitled "The Chemistry of Indoles". Part X: See reference 2.

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3) M. Somei, F. Yamada, and C. Kaneko, Chemistry Lett., 1978, 1249. These compounds are known to have significant pharmacological activities.

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6) Tri-n-butylphosphine is known to catalyze the nucleophilic addition of active methylene compounds to α,β-unsaturated ketones: D.A. White and M.M. Baizer, Tetrahedron Lett., 1973, 3597.

7) ^{1}H-NMR ($CDCl_3$) δ: a) XIIt: 2.17 (3H, s, $C\underline{H}_3CO$), 2.81 (2H, d, J=6 Hz, $C\underline{H}_2CO$), 3.28 (1H, d.d, J=16 and 5.2 Hz, C_3-$\underline{H}_A$), 3.70 (1H, d.d, J=16 and 6.5 Hz, C_3-$\underline{H}_B$), 4.31 (1H, d.d.d, J=6, 6, and 6.5 Hz, C_5-$\underline{H}$), 5.00 (1H, d.d.d, J=5.2, 6.5, and 6.5 Hz, C_4-$\underline{H}_X$), 6.61-7.18 (m, aromatic 4H), 7.93 (1H, br.s., NH). b) XIIc: 2.08 (3H, s, $C\underline{H}_3CO$), 2.78 (2H, d, J=7 Hz, $C\underline{H}_2CO$), 3.45 (2H, d, J=7 Hz, C_3-$\underline{H}_2$), 4.36 (1H, d.t, J=4 and 7 Hz, C_5-$\underline{H}$), 5.03 (1H, d.t, J=4 and 7 Hz, C_4-$\underline{H}$), 6.73-7.27 (m, aromatic 4H), 7.98 (1H, br.s, NH).

8) The results will be reported elsewhere.

9) M. Natsume et al. also reported the synthesis of the corresponding methyl carbamate of XVII. M. Natsume and H. Muratake, Heterocycles, 14, 445 (1980).

10) M. Somei, F. Yamada, and C. Kaneko, Chemistry Lett., 1979, 123.

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