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CHEMICAL INTERCONVERSION OF TRYPTOPHAN AND N'-FORMYLKYNURENINE

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A novel reaction to convert 3-alkyl-2-amino-3H-indol-3-ol to 3-alkylindole is described. The yield was 60-80% for four 2-amino-3H-indol-3-ols examined. With aqueous sodium borohydride, 3-alkyl-2-amino-3H-indol-3-ol was reduced and deaminated predominantly to the corresponding indolin-3-ol, which was then dehydrated to 3-alkylindole in acidic media. Eventually a reaction cycle to interconvert tryptophan and N'-formylkynurenine was established.

In a previous paper, we presented a two-step reaction for the conversion of 3-alkylindole to the corresponding 2-amino-3H-indol-3-ol.[1] At the first step, the indole nucleus of 3-alkylindole was oxidized with ozone to yield alkyl 2-formamidophenyl ketone. The oxidation was almost quantitative when the reaction was carried out in methanol below -70°C.[2] The second step was the cyclization reaction of the alkyl 2-formamidophenyl ketone with cyanide ion to the 2-amino-3H-indol-3-ol. The reaction took place readily in aqueous alkaline media at room temperature and the yield was moderately high for five 3-alkylindoles.[1] In the hetero-ring formation, the cyanide carbon was introduced to the C-2 position of the 3H-indole ring, whereas the formyl carbon derived from the parental indole ring was not. This fact indicates that the C-2 carbon atom of 3-alkylindole is replaceable with an extraneous carbon atom if the 2-amino-3-hydroxy-3H-indole ring is converted to the indole ring under proper conditions. In the present paper, we describe a novel

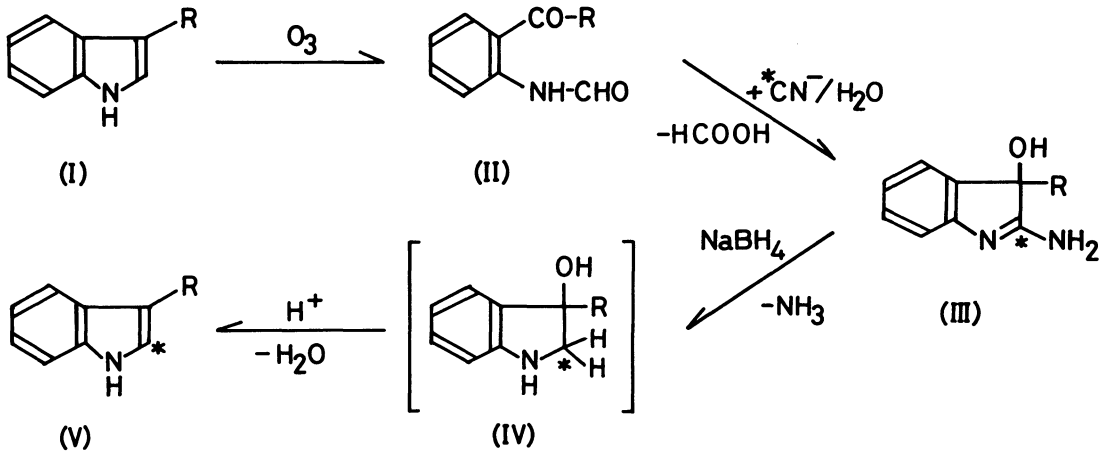

Fig. 1 Elimination and introduction of the C-2 carbon atom in 3-alkylindoles. The cyanide carbon is marked with the asterisk. Suffixes a and b for each compound represent R = $-CH_2CH(NHCOCH_3)COOH$ and $-CH_2CH_2COOH$, respectively (see text).

method for the formation of 3-alkylindoles(V) by acid-catalyzed dehydration after the reduction-deamination of 3-alkyl-2-amino-3H-indol-3-ols(III). The reaction scheme for a whole process including the exchange of the C-2 carbon atom in the indole nucleus is shown in Fig. 1.

A typical experiment for the conversion of 3-alkyl-2-amino-3H-indol-3-ol to 3-alkylindole is described below. N-α-Acetyl-β-(2-amino-3-hydroxy-3H-indol-3-yl)-L-alanine(IIIa, R = $-CH_2CH(NHCOCH_3)COOH$; 280 mg, 1 mmol), which had been prepared from N-α-acetyl-L-tryptophan [M.p. 187-188.5°C. $[\alpha]_D^{23}$ + 28.0° (c 1, as sodium salt in water)] by the method described previously,[1,2] was suspended in water(5 ml) and neutralized with 1 M sodium hydroxide(1 ml). To the resulted solution, sodium borohydride(300 mg, 7.9 mmol) was added in ten parts over a period of 3 hours at room temperature. The solution was then acidified with 1 M hydrochloric acid to pH ~3 and the crystalline leaflets separated were collected after standing overnight at room temperature. Pure N-α-acetyl-L-tryptophan(Va) was obtained by recrystallization from aqueous ethanol in 75% yield(185 mg). M.p. 185-186.5°C. $[\alpha]_D^{23}$ + 27.2° (c 1, as sodium salt in water) (lit.[3], M.p. 189°C. $[\alpha]_D^{31}$ + 29° in the same condition as above). Found: C, 63.60; H, 5.83: N, 11.60%. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38%. M^+(m/e): Found, 246. Calcd., 246. When ^{13}C[90%] enriched(ring C-2)-IIIa was treated under the same conditions, the molecular ion of the final product was detected at m/e 247.

No difference in UV, IR, and ^1H-NMR spectra was observed between the material obtained above and the authentic sample of N-α-acetyl-L-tryptophan. For example, IR spectra of these two materials in KBr discs are shown in Fig. 2.

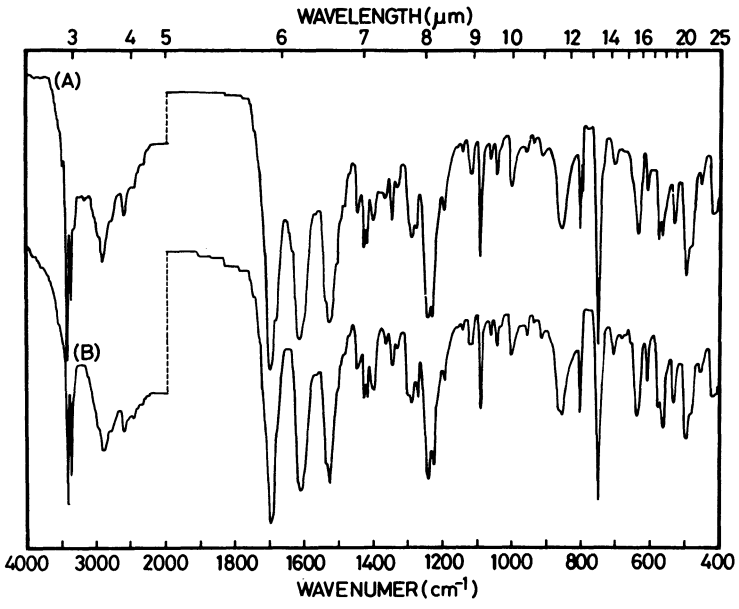

Fig. 2. IR spectra of the deamination-dehydration product (A) of N-α-acetyl-β-(2-amino-3-hydroxy-3H-indol-3-yl)-L-alanine (IIIa) and N-α-acetyl-L-tryptophan(B).

Other 3-alkyl-2-amino-3H-indol-3-ols[1] derived from 3-methylindole, N-α-acetyl-L-tryptophan methylamide, and β-indolepropionic acid were deaminated and dehydrated in the same manner and eventually the parental indole derivatives were

isolated and identified by comparison of the properties with the authentic materials (data not shown). Yields of reduction and dehydration were 60-80% for the above 3-alkyl-2-amino-3H-indol-3-ols.

Reduction of 3-alkyl-2-amino-3H-indol-3-ol was followed by UV and ^{13}C-NMR spectroscopy. Fig. 3 shows a change of UV absorption before and after reduction and dehydration of β-(2-amino-3-hydroxy-3H-indol-3-yl)propionic acid(IIIb, R = -CH_2-CH_2COOH).

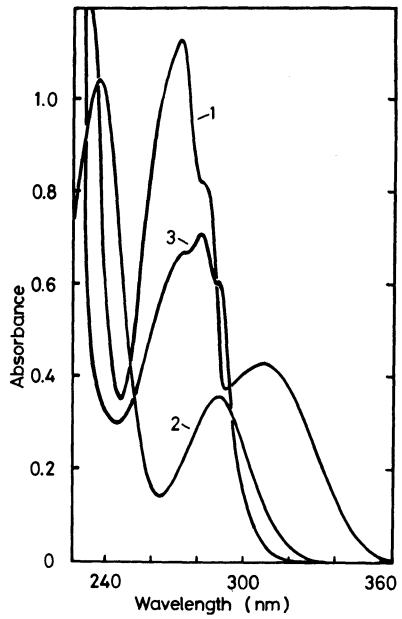

Fig. 3. Change of UV absorption on reduction and subsequent dehydration of β-(2-amino-3-hydroxy-3H-indol-3-yl)propionic acid(IIIb). Curves 1 and 2 represent the spectra of (IIIb) and the reduction product of (IIIb), respectively. Curve 3 was recorded after acidification of the reduction product. All spectra were recorded after dilution with water to about 0.14 mM.

It is obvious that, when the 2-amino-3-hydroxy-3H-indole derivative was reduced with sodium borohydride, (IIIb) was converted to a relatively stable material in alkaline media where the reduction product showed two absorption maxima at 290 and 235 nm with a minimum at 260 nm. The UV absorption(curve 2 in Fig. 3) resembled those of indolines: for example, β-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]-indole-2-carboxylic acid has absorption maxima at 235 and 292 nm and a minimum at 260 nm in water,[4] suggesting that either (IVb) or the 2-amino derivative of (IVb) or both were formed by the reduction of (IIIb).

In ^{13}C-NMR spectroscopy of the reduction mixture of the ^{13}C[90%]-enriched (ring C-2) β-(2-amino-3-hydroxy-3H-indol-3-yl)propionic acid(IIIb), the solitary resonance appeared at δ 58.5 ppm due to the ring C-2 carbon atom with a tiny peak at δ 91.8 ppm(Fig. 4B). The former which appeared as a singlet with complete proton decoupling split to a triplet with off-resonance proton decoupling(Fig. 4A). This finding indicates that there are two protons attached to the ^{13}C-enriched C-2 carbon atom of the main reduction product and suggests that the product is a reduced and deaminated product of (IIIb) that is shown as (IVb) in Fig. 1. Another small peak at δ 91.8 ppm split to a doublet with off-resonance proton decoupling(Fig. 4A). Natural abundance ^{13}C-NMR spectroscopy revealed that, in addition to the expected peaks for the main reduction product (IVb), minor peaks were present with chemical shifts close or identical to those of the carbon atoms of (IVb) (Fig. 4C). These findings suggest the formation of the 2-amino derivative of (IVb) as a minor reduction product, but no attempts have been made to isolate this minor product.

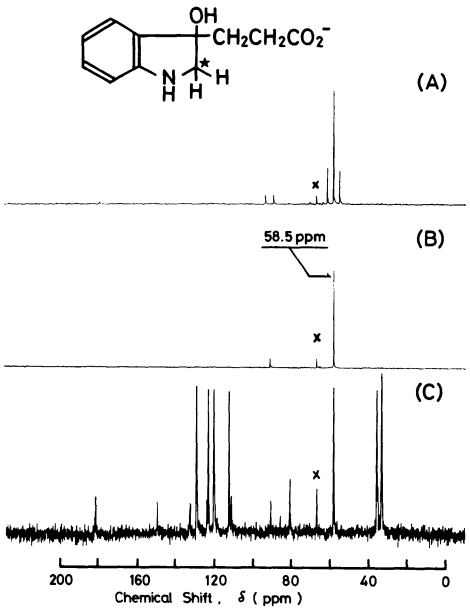

Fig. 4. ^{13}C-NMR spectra of the reduction products of β-(2-amino-3-hydroxy-3H-indol-3-yl)propionic acid(IIIb). Spectra A and B were recorded for the ^{13}C-enriched sample with off-resonance(A) and complete(B) proton decoupling, respectively. Spectrum C is recorded for the non-enriched sample. The peak(x) at δ 67.4 ppm in each spectrum is due to dioxane (internal standard). For the peak at δ 91.8 ppm, see text.

Upon acidification, the UV absorption of (IVb) instantaneously changed to those typical to 3-alkylindoles(Fig. 3). The ^{13}C-NMR spectrum of the reduction mixture of (IVb) after acidification was the same as that of β-indolepropionic acid. For the ^{13}C-enriched compound, the peak at δ 58.5 ppm of (IVb) was shifted to δ 121.4 ppm in $CDCl_3$, which corresponds to the ring C-2 carbon of the indole derivative. In addition, in ^{1}H-NMR spectroscopy of the ^{13}C-enriched β-indolepropionic acid(Vb) in the same solvent, the C-2 proton signal was detected as a doublet at δ 7.0 ppm with coupling constant characteristic of carbon-13[J(^{13}C-H) = 181.3 Hz]. These results show clearly that (IV) is converted to (V) by acid-catalyzed dehydration and that the carbon-13 atom of ^{13}C-enriched cyanide ion used in the ring-closing reaction of (II) is present at the C-2 position in the indole nucleus of (V).

Eventually we established a reaction cycle for an interconversion of tryptophan(3-alkylindole) and N'-formylkynurenine(alkyl 2-formamidophenyl ketone): at the first half of the cycle, tryptophan is quantitatively converted to N'-formylkynurenine by ozone-oxidation and at the second half the latter is reverted to the former by a successive reaction involving the ring-closing reaction with cyanide ion and subsequent deamination-dehydration. In the present study, carbon-13 was exclusively used for isotope labeling of the indole C-2 atom. However, if sodium borohydride that replaced hydrogen with deuterium or tritium was used to reduce (III) to (IV), one may expect to label the C-2 hydrogen with either of these isotopes by a one-flask reaction. That is, the reaction cycle involving the present reduction-deamination provides a novel method to label the carbon and/or hydrogen atoms at the C-2 position in the indole nucleus under mild conditions.

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