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THE SYNTHESIS OF 5- AND 7-ACETYLINDOLE DERIVATIVES. I. THE PHOTOCHEMICAL REARRANGEMENT OF 1-ACETYLINDOLINE

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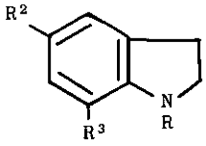
Abstract- 5- and 7-Acetyl substituted indole derivatives have been prepared *via* intramolecular photorearrangement of acyl radical and intermolecular electrophilic acylation of 1-acetylindoline.

The photochemistry of the enamide system and its useful application have been well investigated;[1] simple enamides generally undergo a [1,3]-acyl radical shift to afford vinylogous amides. Meanwhile, photoisomerization of 1-acylindoles of an enamide system have been described to merely provide 2-,3-,4- and 6-acylindoles,[2] and then neither of 5- and 7-acylindoles formed.

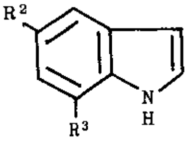
We wish to report here that the photoisomerization of 1-acetylindoline (1) to 5- and 7-acetylindolines or corresponding indoles.[3]

Irradiation of 1-acetylindoline (1) in acetone with a 60-W low pressure mercury lamp in nitrogen atmosphere for 24 h afforded 5- and 7-acetylindolines (2 and 3, in 12% and 11% yields, respectively), together with their corresponding N-acetates (4 and 5) and indole (6). Formation of 2 and 3 is interpreted in terms of a normal rearrangement in analogy with the photo-Fries rearrangement of acetanilides.[4,5]

However, 1,5-diacetylindoline (4, in 2.4% yield) and 1,7-diacetylindoline (5, in 2.5% yield) are abnormal products.[5,6] The structure of these compounds were therefore confirmed by following treatments and spectral data[7] (Table I and II).



	R	R²	R³
1	Ac	H	H
2	H	Ac	H
3	H	H	Ac
4	Ac	Ac	H
5	Ac	H	Ac



	R²	R³
6	H	H
7	Ac	H
8	H	Ac

Table I. ^{1}H-NMR Chemical Shifts (ppm) of 1-5

Compounds	1	2	3	4	5
C(2)-H	4.44(2H) (t,J=9Hz)	4.26(2H) (t,J=9Hz)	4.24(2H) (t,J=9Hz)	4.40(2H) (t,J=9Hz)	4.63(2H) (t,J=9Hz)
C(3)-H	3.46(2H) (t,J=9Hz)	3.58(2H) (t,J=9Hz)	3.54(2H) (t,J=9Hz)	3.45(2H) (t,J=9Hz)	3.60(2H) (t,J=9Hz)
C(4)-H	7.44(3H) 4,5,6-H (m)	8.25(1H) (d,J=2Hz)	7.88(1H) (d,J=9Hz)	8.08(1H) (d,J=2Hz)	7.46(1H) (d,J=9Hz)
C(5)-H		----	7.83(1H) (t,J=9Hz)	----	7.60(2H) 5,6-H(m)
C(6)-H		8.21(1H) (dd,J=9;2Hz)	8.17(1H) (dd,J=9;2Hz)	8.10(1H) (dd,J=9;2Hz)	
C(7)-H	8.10(1H) (d,J=9Hz)	7.75(1H) (d,J=9Hz)	----	8.34(1H) (d,J=9Hz)	----
NCOMe	2.79(s)	----	----	2.61(s)	2.30(s)
CCOMe	----	2.84(s)	2.88(s)	2.80(s)	2.66(s)

Run at 300 MHz in CF$_3$COOD solution.

Table II. ^{13}C-NMR Chemical Shifts (ppm) of 1-5

Compounds	1	2	3	4	5
C(2)	48.70	47.18	46.62	49.18	49.51
C(3)	27.93	28.79	27.90	27.51	29.03
C(4)	124.51	125.79	115.75	124.51	124.99
C(5)	123.53	156.29	115.27	146.96	124.37
C(6)	127.43	127.85	128.14	129.51	126.45
C(7)	116.87	106.98	154.04	116.02	137.52
C(3a)	131.11	128.87	128.50	131.68	131.56
C(7a)	142.89	130.35	131.54	132.74	133.76
NCOMe	168.68	------	------	169.33	168.29
NCOMe	24.19	------	------	24.31	23.52
CCOMe	------	196.47	199.09	196.95	200.41
CCOMe	------	26.13	26.56	26.50	28.83

Run at 75.44 MHz in CDCl$_3$ solution.

The compounds 2 and 3 were easily converted to 4 and 5 by treatment with acetic anhydride. Hydrolysis of 4 and 5 with methanolic hydrochloride readily gave 2 and 3, respectively. The structure of 2, 3, 4 and 5 were assigned by comparing those uv and nmr spectra with those of the analogous ketoamines (II and III)[5] and ketoamides (IV and V).[6]

It is generally believed that the photo-Fries rearrangement is an intramolecular reaction.[8,9] However, occurrence of 4 and 5 in our case clearly indicated that a part of the reaction proceed in an intermolecular fashion. Therefore, the reaction mechanism could be interpreted as follows. Thus, irradiation of 1 produced acetyl and indolyl radicals and subsequent recombination of them in a solvent cage[8] afforded 2 and 3. Further intermolecular reaction of 2 and 3 with an another acetyl radical, which was generated either by the other molecule (1) or by the Norrish type I fission of acetone used as a solvent, afforded 4 and 5.

Further confirmation of the structures 4 and 5 was carried out by comparing these uv and nmr spectra with those of the following Friedel-Crafts products.

The acylation (the condition, 1 : $AlCl_3$: AcCl = 1 : 3 : 3)[10] of 1 afforded 4 and 5 in the ratio of 93 : 7 in 80.8% yield.

In addition, the irradiation of 2 and 3 in acetone solution for 70 h afforded 5-acetylindole (7) and 7-acetylindole (8)[11] in 90% and 95% yields, respectively, and then formation of 4 and 5 was not detected by acetyl radical from acetone.

The compounds 2 and 3 were also converted by means of Pd-C dehydrogenation to 7 and 8 in 51% and 76% yields,[12,13] respectively.

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5.The photoisomerization of 2-methylacetanilide (mp 112-114°C, M^+:m/z 149) afforded 2-methyl-4-acetylaniline (II)(mp 108-109°C, M^+:m/z 149), which was acylated with acetic anhydride to 2-methyl-4-acetylacetanilide (IV)(mp 153-154°C, M^+:m/z 191).

6.2-Acetyl-4-methylaniline (III)(mp 35°C, M^+:m/z 149) and 2-acetyl-4-methylacetanilide (V)(mp 123-124°C, M^+:m/z 191) were formed simultaneously by photochemical rearrangement of 4-methylacetanilide (mp 149-150°C, M^+:m/z 149) in acetone.

7.Compound 1:mp 104-105°C (ether), M^+:m/z 161 ($C_{10}H_{11}ON$), 188 (base peak), uv λ EtOH/max. 206, 252, 281, 290nm., ir ν Nujol/max. 1645, 1600cm^{-1}.

Compound 2:mp 76-77°C (ether), M^+:m/z 161 ($C_{10}H_{11}ON$), 146 (base peak), 118. uv λ EtOH/max. 206, 244, 337nm., ir ν Nujol/max. 3270, 1635, 1580cm^{-1}.

Compound 3:mp 85-86°C (ether), M^+:m/z 161 ($C_{10}H_{11}ON$) (base peak), 146, 118. uv λ EtOH/max. 234, 259, 380nm., ir ν Nujol/max. 3380, 1630, 1610, 1575cm^{-1}.

Compound 4:mp 140-141°C (EtOH), M^+:m/z 203 ($C_{12}H_{13}O_2N$) (base peak), 188, 161, 146, 118., uv λ EtOH/max. 206, 312nm., ir ν Nujol/max. 1685, 1645, 1590, 1580cm^{-1}.

Compound 5:mp 126-127°C (EtOH), M^+:m/z 203 ($C_{12}H_{13}O_2N$), 161 (base peak),146, 118. uv λ EtOH/max. 226, 256, 304nm., ir ν Nujol/max. 1680, 1640, 1585cm^{-1}.

Compound 6:mp 52-53°C (n-Hexane), M^+:m/z 117 (C_8H_7N), uv (EtOH) characteristic indole chromophore.

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11.Indoline was easily dehydrogenated by irradiation in acetone solution to indole.

12.Compounds 4 and 5 were not converted to indole derivatives neither by Pd-C dehydrogenation reaction nor by irradiation in acetone solution.

13.Compound 7:bp $_2$155°C, uv λ EtOH/max. 205, 250, 297nm., ir ν film/max. 3300, 1650, 1600cm^{-1}. ^{1}H-nmr($CDCl_3$) δ(ppm) 2.66(s,CH_3), 7.26(d,J=3 Hz,C_2-H), 6.38(d,J=3 Hz, C_3-H), 8.32(d,J=2 Hz,C_4-H), 7.85(dd,J=8 ; 2 Hz,C_6-H), 7.39(d,J=8 Hz,C_7-H),9.24(NH).

Compound 8:mp.65-66°C (n-Hexane), uv λ EtOH/max. 203, 225,236, 240, 330nm. ir ν Nujol/max. 3370, 1640, 1580cm^{-1}. ^{1}H-nmr($CDCl_3$) δ(ppm) 2.70(s,CH_3), 7.32(d,J=3 Hz, C_2-H),6.58(d,J=3Hz,C_3-H),7.77(d,J=8Hz,C_4-H),7.16(t,J=8Hz,C_5-H),7.89(d,J=8Hz,C_6-H).

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