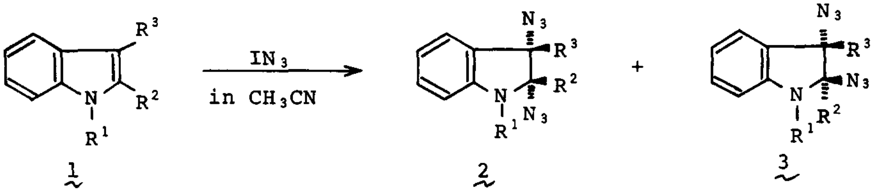
Tetrahedron Letters No. 38, pp 3291 - 3294, 1975. Pergamon Press. Printed in Great Britain.

REACTION OF IODINE AZIDE WITH 1-ACYLINDOLES: FORMATION OF 1-ACYL-*cis*- AND *trans*-2,3-DIAZIDOINDOLINES

Yasumitsu Tamura, Sundo Kwon, Fujio Tabusa, and Masazumi Ikeda
Faculty of Pharmaceutical Sciences, Osaka University,
133-1, Yamada-kami, Suita, Osaka, Japan

(Received in Japan 5 July 1975; received in UK for publication 12 August 1975)

Iodine azide (IN_3) is known to undergo addition to a number of olefins with stereo- and regio-specificity to give organic azides.[1] We have now found that reaction of IN_3 with 1-acylindoles gives rise to remarkably stable 1-acyl-*cis*- and *trans*-2,3-diazidoindolines in high yields,[2] which would be useful in the syntheses of indole derivatives of potential pharmacological activity.



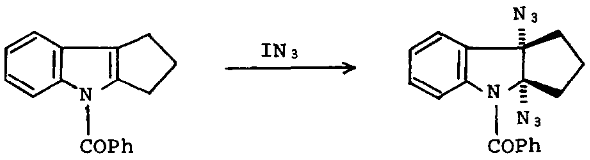
a) R^1=COPh, R^2=H, R^3=Me; b) R^1=COPh, R^2=R^3=H; c) R^1=COPh, R^2=R^3=Me;
d) R^1=$SO_2C_6H_4CH_3$(*p*), R^2=H, R^3=Me; e) R^1=CO_2Et, R^2=H, R^3=Me

Treatment of 1-benzoyl-3-methylindole (1a) (1.7 mmole) with IN_3 prepared *in situ* from iodine monochloride (3.5 mmole) and sodium azide (4.3 mmole) in dry acetonitrile (10 ml) at room temperature gave 91% yield of a mixture of two isomeric products in a ratio of 2:7 (by nmr spectroscopy). The products could be separated by a combination of recrystallization and chromatographical technique to give 2a, mp 130-131°,[4] and 3a, mp 47.5-49°, whose structures were assigned on the basis of the following evidence. Microanalysis and mass spectrometry (*m/e* 319, M^+) of 2a confirmed the molecular formula, $C_{16}H_{17}N_7O$. The ir spectrum showed a strong azide absorption band at 2100 cm^{-1} and the nmr spectrum showed a singlet at δ 5.59 (2-H), a methyl singlet at δ 1.60, and a multiplet for the remaining aromatic hydrogens between δ 6.8 and 7.9. Reduction of 2a with lithium aluminum hydride gave 1-benzyl-3-methylindole (4).[5] Since the ir, nmr and mass spectra of compound 3a were strikingly similar to those of 2a and since lithium aluminum hydride reduction of 3a also gave 4, 3a is isomeric with 2a. The cis stereochemistry about two azido groups in 2a and the trans stereochemistry in 3a were assigned on the basis of a comparison of the chemical shifts of the 3-methyl signals. The 3-methyl group in 3a lies in parallel to the 2-azido group and should be deshielded relative to the 3-methyl group in 2a.[6] Indeed, the 3-methyl group in 3a occurs at 0.15 ppm lower field than that in 2a.

Similarly, 1-benzoylindole (1b), 1-benzoyl-2,3-dimethylindole (1c), 1-tosyl-3-methylindole (1d), and 1-ethoxycarbonyl-3-methylindole (1e) gave the corresponding cis and trans diazides; the structures and stereochemistry were assigned by ir, mass, and nmr spectroscopic data (Table 1). Assignments of the spacial relationship of two azido groups in 2b and 3b were tentatively made on the basis of comparison of the spin-coupling pattern between 2-H and 3-H (J_{23}=6 Hz for 2b and J_{23}=0 Hz for 3b).[7]

In contrast, the reaction of 1-benzoyl-2,3-trimethyleneindole (5) gave only cis adduct 6, mp 146-148°, in 89% yield, whose stereochemical assignment was made by inspection of the molecular models; the trans fused 5-5 ring system is too strained to permit their formation.

The diazides obtained above are surprisingly stable to heat; for example, 3b was recovered unchanged after refluxing for 8 hr in toluene.



5 6

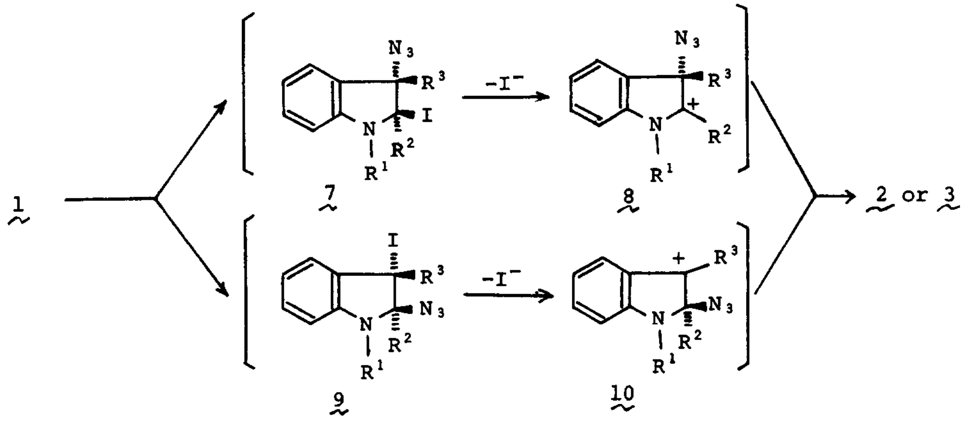
Table 1. Physical Data of 1-Acyl-2,3-diazidoindolines

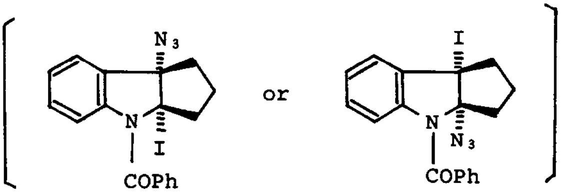
Reactant	Total Yield (%) [Product Ratio (2:3)[a]]	Product 2[b] mp(°C)[c]	Product 2[b] nmr (δ)[d]	Product 3[b] mp(°C)[c]	Product 3[b] nmr (δ)[d]
1a	91 [2:7]	130-131	5.59(2-H) 1.60(3-CH_3)	47.5-49	5.63(2-H) 1.75(3-CH_3)
1b	80 [2:7]	136-138	5.97(2-H) 4.98(3-H)	oil	5.82(2-H) 4.54(3-H)
1c	96 [1:1]	87-89	1.91(2-CH_3) 1.60(3-CH_3)	110-111	2.07(3-CH_3) 1.70(3-CH_3)
1d	93 [1:2]	130-132	5.36(2-H) 1.02(3-CH_3)	133-135	5.36(2-H) 1.59(3-CH_3)
1e	92 [1:2]	oil	5.57(2-H) 1.70(3-CH_3)	oil	5.57(2-H) 1.48(3-CH_3)

a) The ratio of products was determined by nmr spectroscopy. b) All crystalline compounds were recrystallized from methanol. c) Measured in deuterochloroform using tetramethylsilane as internal standard. d) All the trans isomers showed larger Rf-values than the corresponding cis isomers.

Attempts to gain the normal 1:1 adduct 5 or 6 were unsuccessful; for example, the reaction of equimolar quantities of 1a and IN_3 resulted in the formation of a mixture of the diazides 2a and 3a, and unreacted starting material.

A mechanistic rationalization of the non-stereospecific formation of the diazides 2a-e and 3a-e is based on the premise that the initially formed adduct 7 or 9 undergoes carbon-iodine bond cleavage followed by attack of azide anion to the resulting carbonium ion 8 or 10 (S_N1 mechanism) to give 2 and 3. On the other hand, the formation of 6 may involve syn addition of IN_3[8] to give 11. This step is then followed by substitution (S_N1 mechanism) of iodine by N_3. The steric restrain of the ring system may account for the specific formation of the cis isomer.





11

Finally, it should be noted that the reaction of IN_3 with indole gave a mixture consisting of at least four products.

References and Footnotes

1. A Hassner, Accounts Chem. Res., 4, 9 (1971).
2. The formation of diazides by the reaction of IN_3 with olefins was first reported by Sasaki and coworkers,[3] who obtained unstable *cis*-diazides from medium-membered olefins such as cyclooctatetraene, tropone ethyleneketal, and 1-ethoxycarbonyl-1(1H)azepine.
3. T. Sasaki, K. Kanematsu, and Y. Yukimito, J. Org. Chem., 37, 890 (1972); J. C. S. Perkin I, 375 (1973).
4. All new crystalline compounds gave satisfactory elemental and spectral analyses.
5. The exact mechanism of the formation of 4 is not clear at present.
6. A. Hassner, J.E. Kropp, and G.J. Kent, J. Org. Chem., 34, 2628 (1969).
7. F.A.L. Anet and J.M. Muchowski, Chem. and Ind. (London), 81 (1963).
8. G. Mehta, P.K. Dutta, and P.N. Pandy, Tetrahedron Letters, 445 (1975).