THE FISCHER INDOLE SYNTHESIS WITH FORMIC ACID. III.[1a] THE REACTION WITH 2-SUBSTITUTED ADIPOINS.

Takeshi Wakamatsu*, Hiromu Hara, and Yoshio Ban
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

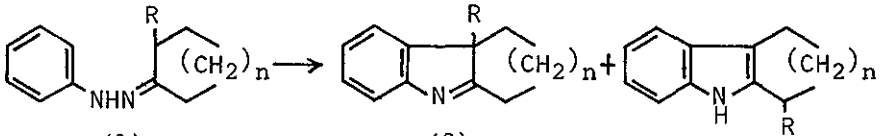
The Fischer indolization of 2-substituted adipoins was effected with formic acid to afford 1-substituted tetrahydrocarbazoles (9) and the corresponding carbazoles (10).

Various procedures including thermal cyclization are available for the Fischer indole synthesis, which has been regarded as a most versatile method for preparation of indoles.[2]

In the Fischer indole synthesis of 2-substituted cycloalkanone arylhydrazones (1) with acid catalyst, there is produced a mixture of indolenine (2) and indole (3), the relative quantities of which have been found to be dependent upon the nature of the utilized catalyst.[3,4]

It was demonstrated in this laboratory that anhydrous formic acid could be used as an effective catalyst for the above indolization.[1] The reaction with this catalyst smoothly occurred

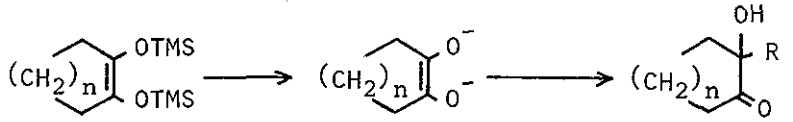
to provide the indolenine (2) predominantly rather than the indole (3). But, it has been also experienced in other reactions with formic acid that generation of the indole (3) is in preference to formation of the indolenine (2).[5]



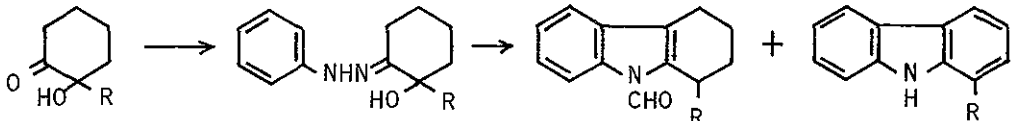
(1) (2) (3)

Thus, it is generally difficult to control the direction of cyclization of 2-substituted cycloalkanone arylhydrazones.

We now report that the Fischer indolization of 2-substituted adipoins (7) readily prepared from enediol-bis-trimethylsilyl ether (4) through 1,2-enediolate (5)[6] led only to the exclusive formation of the indoles (9) and (10) instead of the indolenine (2) type, whose reaction should be regarded as an equivalent to the controlled Fischer indolization of 2-substituted cyclohexanones.



(4) (5) n=1,2,3 (6)



(7) (8) a, R=CH_3 b, R=CH_2CH_3 c, R=CH_2Ph (9) (10)

A solution of the phenylhydrazone (8a) freshly prepared from 2-methyladipoin (7a) and phenylhydrazine in 98-100% formic acid was refluxed with stirring for 1 hr. The neutral material was purified by chromatography on silica gel using ethyl acetate/ n-hexane (1:10) as eluent to yield 1-methyl-N-formyl-tetrahydrocarbazole (9a) [mp 97-99°;ir (Nujol) 1695 cm^{-1};uv λ_{max}^{EtOH} nm (ε) 248 (15600),300 (3820);nmr ($CDCl_3$) δ 1.35 (3H,d,J=7Hz),8.20 (1H, s),9.25 (1H,s);m/e 213 (M^+)] and 1-methylcarbazole (10a) [mp 122-123°(lit.[7] 118-119°);ir (Nujol) 3410 cm^{-1};nmr ($CDCl_3$) δ 2.43 (3H, s);m/e 181 (M^+)] in 15% and 16% yields, respectively. The structural assingment of (9a) was confirmed by dehydrogenation to the known compound (10a) with palladium-on-carbon in refluxing p-cymene. In a similar manner, 2-ethyladipoin (7b) gave (9b) [13%;mp 79-80°,ir (Nujol) 1690 cm^{-1};uv λ_{max}^{EtOH} nm (ε) 248 (14000), 301 (3660);nmr ($CDCl_3$) δ 1.05 (3H,t,J=7Hz),8.18 (1H,s),9.25 (1H, s);m/e 227 (M^+)] and (10b) [13%;mp 74-75°(lit.[8] 73-74°);ir (Nujol) 3420 cm^{-1};nmr ($CDCl_3$) δ 1.39 (3H,t,J=8Hz),2.90 (2H,q,J=8Hz);m/e 195 (M^+)]. Also, 2-benzyladipoin (7c) afforded (9c) [8%;mp 101-103°;ir (Nujol) 1700 cm^{-1};uv λ_{max}^{EtOH} nm (ε) 250 (19300)nmr ($CDCl_3$) δ 8.18 (1H,s),9.36 (1H,s);m/e 289 (M^+)] and (10c) [20%;mp 148-149°;ir (Nujol) 3412 cm^{-1};uv λ_{max}^{EtOH} nm (ε) 216 (31900),238 (35500), 259 (20100),293 (14500),326 (3890),338 (3450);nmr ($CDCl_3$) δ 4.30 (2H,s);m/e 257 (M^+)]. The formation of the equal amounts of (9) and (10) in the present reactions except for the case of the benzyl derivative (7c) seems to be a result of disproportionation of 3,4-dihydrocarbazoles in the course of indolization.

ACKNOWLEDGMENT This work was supported by a Grant-in-Aid for Scientific Research (No. 877340) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

REFERENCES

1 a) Part II, J. Shimizu, S. Murakami, T. Oishi, and Y. Ban, Chem. Pharm. Bull. (Tokyo), 19, 2561 (1971); b) Y. Ban, T. Oishi, Y. Kishio, and I. Iijima, Chem. Pharm. Bull. (Tokyo), 15, 531 (1967).

2 a) E. Fischer, Chem. Ber., 19, 1563 (1886); Justus Liebigs Ann. Chem., 236, 116 (1886); B. Robinson, Chem. Rev., 63, 373 (1963); ibid., 69, 227 (1969).

3 a) K. H. Pausacker, J. Chem. Soc., 621 (1950); b) J. McLean and R. I. Reed, ibid., 2519 (1955).

4 Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, Chem. & Ind. (London), 473 (1965).

5 a) Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, Tetrahedron Letters, 3383 (1968); b) M. Ikezaki, T. Wakamatsu, and Y. Ban, Chem. Commun., 88 (1969); c) M. Akagi, T. Oishi, and Y. Ban, Tetrahedron Letters, 2063 (1969).

6 T. Wakamatsu, M. Fukui, and Y. Ban, Synthesis, 341 (1976).

7 D. P. Chakraborty, K. C. Das, and S. P. Basak, J. Indian Chem. Soc., 45, 84 (1968).

8 R. H. F. Manske and M. Kulka, Can. J. Research, 443 (1950).

Received, 5th August, 1977