Acylation of Indoles by Duff Reaction and Vilsmeier–Haack Formylation and Conformation of *N*-Formylindoles

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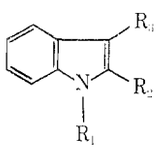
Indoles react with hexamethylenetetramine to give 3-formylindoles. Skatole on formylation with *N,N*-dimethylformamide and phosphorus oxychloride gives 1-formyl-3-methylindole, 2-formyl-3-methylindole, and *o*-formamidoacetophenone. The same reaction with 2,3-dimethylindole gives 2,3-dimethyl-1-formylindole. 1-Formylindole exists in two conformations in CCl_4 at 30° while, under the same conditions, 2,3-dimethyl-1-formylindole exists solely in one conformation.

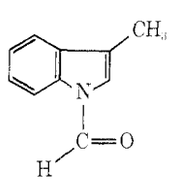
Phenolic compounds are known to undergo Duff reaction with hexamethylenetetramine (HMT) and give the corresponding phenolic aldehydes.[1] It was of interest to study the possibility of formylation of indoles with this reagent. Formylation of indoles by Vilsmeier–Haack reaction and acylation of organometallic derivatives of indoles and 3-substituted indoles are well documented,[2] but extensive investigation of the former reaction with 3-substituted indoles has not been carried out so far.[2a] It was also considered worthwhile to study this reaction on 3-substituted indoles. The results of these studies as well as that of an investigation on the conformational aspect and aldehydic character of *N*-formylindoles are presented in this communication.

The action of HMT on **1** and **2** in hot AcOH resulted in the formation of the indole-3-carboxaldehydes **3** and **4** in 25 and 74% yields, respectively. The yields are lower than those of the Vilsmeier–Haack formylation of indoles. However, the reaction is extremely easy and convenient to perform. It may be mentioned in this connection that no trace of **3** was found in a similar reaction under milder conditions.[3]

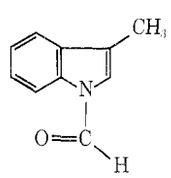
The Vilsmeier–Haack formylation of **5** and **6** was studied and the results are given in Tables I and II.



Compd	R_1	R_2	R_3
1	H	H	H
2	H	C_6H_5	H
3	H	H	CHO
4	H	C_6H_5	CHO
5	H	H	CH_3
6	H	CH_3	CH_3
7	H	$COCH_3$	CH_3
9	H	CHO	CH_3
12	$CH{=}NNHC_6H_3(NO_2)_2$ (*o,p*)	H	CH_3
13	$CH{=}NNHC_6H_3(NO_2)_2$ (*o,p*)	CH_3	CH_3



8a



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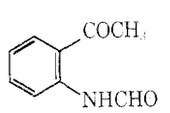

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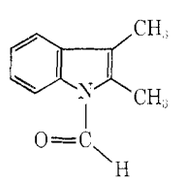

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TABLE I

PRODUCTS FROM THE REACTION OF 5 WITH *N,N*-DIMETHYLFORMAMIDE (DMF) AND $POCl_3$ UNDER DIFFERENT CONDITIONS

Temp, °C	Time, hr	Yield,[a] % 8	9	10	5
98–100	3	71	22.5	0.5	Nil
28–30	3	34	11	Nil	52
28–30	36	38	15	1	45
28–30	150	41	19	2.3	35

[a] Actual yield of the products isolated by column chromatography on silica gel.

The yields of all the products increased considerably at elevated temperature, and the *N*-formyl derivative was the major product.[4–6] However, BF_3-catalyzed acetylation of **5** with Ac_2O–AcOH in boiling ether for 5 min

TABLE II

PRODUCTS FROM THE REACTION OF 6 WITH DMF AND $POCl_3$ UNDER DIFFERENT CONDITIONS

Temp, °C	Time, hr	Yield,[a] % 11	6
98–100	6	52.1	0.55
28–30	48	15	65

[a] See footnote *a*, Table I.

(1) (a) L. N. Ferguson, *Chem. Rev.*, **38**, 230 (1946); (b) C. F. H. Allen and G. W. Leubner, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 866; (c) W. E. Smith, *J. Org. Chem.*, **37**, 3972 (1972).

(2) (a) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 33–39, 412–417; (b) W. A. Remers and R. K. Brown in "The Chemistry of Heterocyclic Compounds," Vol. 25, Part 1, W. J. Houlihan, Ed., Wiley-Interscience, New York, N. Y., 1972, pp 116–120, 133–134; (c) R. A. Heacock and S. Kasparek in "Advances in Heterocyclic Chemistry," Vol. 10, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1969; (d) D. E. Horning and J. M. Muchowski, *Can. J. Chem.*, **48**, 193 (1970).

(3) H. R. Snyder, S. Swaminathan, and H. J. Sims, *J. Amer. Chem. Soc.*, **74**, 5110 (1952).

(4) It was reported that the yield of **8** remained the same, while that of **9** decreased with increasing temperature of a similar reaction: C. W. Whittle and R. N. Castle, *J. Pharm. Sci.*, **52**, 645 (1963).

(5) A recent report appears to indicate that **8** and **9** were formed in the ratio of 95:5 in the Vilsmeier–Haack formylation of **5**: S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc., Chem. Commun.*, 427 (1972).

(6) **11** was obtained from **6** in 30.4% yield in a slightly different reaction: N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **27**, 1049 (1957); *Chem. Abstr.*, **52**, 3763 (1958).

afforded only the 2-acetylindole **7** [mp 147°; ir 3320 (NH), 1645 cm^{-1} (C=O)] in 88% yield.[7]

The nitrogen of indole is very weakly basic because of delocalization of its lone pair of electrons to make up the ten-electron π system. These electrons of *N*-acylindoles are not fully available for entering into conjugation with the acyl group as in typical amides and formamides. It was, therefore, hoped that *N*-acylindoles would show some carbonyl character. With this view in mind, the *N*-formylindoles **8** and **11** were treated with 2,4-dinitrophenylhydrazine (DNP) in weakly acidic media, and they were, in fact, found to form the DNP derivatives **12** and **13**, exhibiting thereby pronounced carbonyl character of their *N*-formyl groups. However, in the highly acidic medium usually employed in such reactions,[8] the *N*-formyl groups of **8** and **11** were readily cleaved off, and the DNP derivatives could not be isolated from such reaction media. In this connection, it may be pointed out that such carbonyl character of an amido or formamido group does not appear to have been observed before.[9]

Products of the type **10**, which was also prepared by perbenzoic acid oxidation of **5**[10] for direct comparison, do not appear to have been obtained before in the Vilsmeier–Haack formylation of indoles. Perhaps it arises out of aerial oxidation.

From nmr spectral studies, certain *N*-acylindolines were shown to exist in two conformations.[11] Similar investigation on *N*-acylindoles does not appear to have been made so far. Analysis of the nmr spectra of **8** and **11** in CCl_4 at 31.5° revealed that under these conditions **8** exists in two different conformations, whereas **11** exists in only one. The aldehydic proton of **11** appeared as a singlet at δ 9.04, indicating that it exists solely in the conformation shown in its structural formula, because of the buttressing effect of the 2-CH_3 group. The same proton of **8** gave rise to two singlets at δ 8.78 and 9.08 accounting for 75 and 25% of one proton, respectively. Thus, **8** exists in two conformations **8a** and **8b**, **8a** being predominant because of the lack of a buttressing group at the 2 position. The 7-H of **8** and **11** gave rise to a broad doublet at δ 8.88 (J = 7 Hz, ortho coupling) and a broad hump at δ 8.12, respectively, due to the deshielding effect of the magnetic anisotropy of the C=O group. The aldehydic proton and the 7-H of **9** appeared as a singlet at δ 10.02 and as a doublet at δ 7.70 (J = 7 Hz), respectively.

The uv spectra of the formylindoles and their DNP derivatives are recorded in Table III.

TABLE III

UV SPECTRA OF FORMYLINDOLES AND THEIR DNP DERIVATIVES

	λ_{max}, mμ (log ϵ_{max}), in EtOH
1-Formylindole **8**	240 (4.53), 292 (3.79), 298 (3.78)
1-Formylindole **11**	247 (4.32), 300 (3.68)
2-Formylindole **9**	238 (4.17), 312 (4.33)
DNP derivative **12**[a]	256 (4.25), 304 (3.82), 314 (3.84), 392 (4.40)
DNP derivative **13**[a]	227 (4.55), 253 (4.34), 316 (4.07), 391 (4.40), 410 (4.35)

[a] In THF.

Experimental Section

Melting points are uncorrected. Light petroleum refers to the fraction boiling at 60–80°. Ir spectra were recorded in Nujol mulls and nmr spectra in $CDCl_3$, if not mentioned otherwise. Chemical shifts are given in δ values relative to TMS. DMF and $POCl_3$ were distilled immediately before use.

Indole-3-carboxaldehyde (**3**).—A mixture of indole (0.35 g), HMT (1 g), and glacial AcOH (1.5 ml) was heated at 100° for 2.5 hr. Concentrated HCl (2.5 ml) in water (3 ml) was added and heating was continued for 10 min more. Water (15 ml) was added, the mixture was neutralized with $NaHCO_3$, and the resulting solids were collected. A light brown mass was obtained by extracting both the filtrate and the residue with AcOEt. After crystallization from AcOEt–light petroleum and finally from EtOH, it afforded **3** (108 mg, 25%), ir 3175 (NH), 1630 cm^{-1} (C=O), as almost colorless needles, mp 196–198°. Its identity was confirmed by mixture melting point determination and tlc comparison with an authentic sample.

2-Phenylindole-3-carboxaldehyde (**4**) was prepared from 2-phenylindole[12] (2.12 g), HMT (3.65 g), and glacial AcOH (5.5 ml) following the foregoing procedure and obtained after crystallization from EtOH as pale yellow solids (1.80 g, 74%): mp 251–252° (lit.[2d] mp 251–252°); ir 3160 (NH) and 1635 cm^{-1} (s, C=O). Aldoxime: colorless needles (from benzene); mp 182–184° (lit.[3] mp 182–184°); ir 3280, 3460 (NH, OH), 1640 cm^{-1} (w, C=N).

Formylation of Skatole (**5**).—$POCl_3$ (1.25 ml) was added dropwise with stirring to DMF (4.25 ml) at 10–20° over 20 min. **5** (1.64 g) in DMF (1 ml) was added slowly with stirring and the mixture was heated for 3 hr at 98–100°. Excess concentrated aqueous solution of NaOAc was added. The mixture was stirred for 30 min at 28° and extracted with AcOEt (3 × 20 ml). The dried ($MgSO_4$) extract after removal of solvent furnished a pale yellow oil (1.95 g) which was chromatographed on a silica gel column. Elution with light petroleum–ether (19:1) afforded ***N*-formyl-3-methylindole** (**8**, 1.41 g, 71%) as a colorless oil [lit.[4] bp 98–100° (0.03 mm)]: ir (neat) 1690 cm^{-1} (NCHO); mass spectrum (70 eV) m/e (rel intensity) 159 (70, M^+), 131 (20, M − CO), 130 (100, 131 − H). Further elution of the column with light petroleum–ether (17:3) first gave **3-methylindole-2-carboxaldehyde** (**9**, 0.45 g, 22.5%) as almost colorless needles (from light petroleum): mp 138–140° (lit.[4] mp 139–140°); ir 3340 (NH) and 1648 cm^{-1} (C=O). Latter fractions furnished ***o*-formamidoacetophenone** (**10**, 10 mg, 0.5%) as almost colorless needles (from cyclohexane): mp 77° (lit.[10] mp 77°); nmr (HA 100 MHz) 8.71 (b d, 1, NCHO, J = 8 Hz), 8.46 (b s, 1, NH), 7.89 (d, 1, ArH ortho to $COCH_3$, J = 8 Hz), 7.86 (d, 1, ArH ortho to NCHO, J = 8 Hz), 7.53 (*ca.* t, 1, ArH para to $COCH_3$, J = 8 Hz), 7.13 (*ca.* t, 1, ArH para to NCHO, J = 8 Hz), and 2.64 (s, 3, $COCH_3$); mass spectrum (70 eV) m/e (rel intensity) 163 (43, M^+), 148 (17), 135 (53), 120 (100), 92 (33), 43 (28).

2,3-Dimethyl-*N*-formylindole (**11**) was prepared from **6**[12] (4.5 g), $POCl_3$ (5.45 g), and DMF (10 g), following the foregoing procedure except that the reaction mixture was heated at 98–100° for 6 hr under N_2. The crude product on chromatography over silica gel in benzene–light petroleum (1:1) gave unreacted **6** (25 mg) together with **11** (2.80 g, 52.1%) as colorless needles (from cyclohexane), mp 87–88° (lit.[6] mp 84–86°), ir 1700 cm^{-1} (NCHO).

2,4-Dinitrophenylhydrazone 12 of *N*-Formyl-3-methylindole (**8**).—**8** (159 mg) in MeOH (4 ml) was added to a clear, weakly acidic solution of DNP (198 mg) in MeOH (10 ml). After 1 hr, **12** (275 mg) was collected, crystallized from THF, and obtained as orange-red needles: mp 278° dec; ir 3213 (NH), 1613 cm^{-1} (C=N); mass spectrum (70 eV) m/e (rel intensity) 339.2 (16.66, M^+), 159.1 (13.43), 131.2 (45.34), 130.2 (100), 103.2 (16.58), 77.1 (25.05).

Anal. Calcd for $C_{16}H_{13}N_5O_4$: C, 56.6; H, 3.9; N, 20.6. Found: C, 56.9; H, 3.9; N, 20.5.

(7) (a) A. E. Smith, Ph.D. Thesis, University of Liverpool, 1963; (b) K. M. Biswas, Ph.D. Thesis, University of Liverpool, 1967.

(8) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1964, pp 344, 722.

(9) The *N*-acetyl group of an acylindole was reported to be inert to DNP and similar other reagents: H. Plieninger and K. Suhr, *Chem. Ber.*, **89**, 270 (1956).

(10) B. Witkop, *Justus Liebigs Ann. Chem.*, **558**, 91 (1947).

(11) R. P. Ryan, W. G. Lobeck, Jr., C. M. Combs, and Y.-H. Wu, *Tetrahedron*, **27**, 2325 (1971), and references cited therein.

(12) Prepared by the method of H. M. Kissman, D. W. Farnsworth, and B. Witkop, *J. Amer. Chem. Soc.*, **74**, 3948 (1952).

2,4-Dinitrophenylhydrazone 13 of 2,3-Dimethyl-*N*-formylindole (11).—Concentrated H_2SO_4 (2 drops) was added cautiously to a boiling suspension of DNP (0.1 g) in MeOH (3.5 ml) until a clear solution was obtained, and 11 (86 mg) in MeOH (3 ml) was mixed with it. After the mixture was cooled at 0° for 4 hr, **13** (0.1 g) was collected, crystallized from THF, and obtained as brilliant red, hairy needles: mp 266° dec; ir 1640 cm^{-1} (C=N); mass spectrum (70 eV) *m/e* (rel intensity) 354 (15.90, M + 1), 353 (82.55, M^+), 171 (32.01), 145 (47.13), 144 (100), 143 (34.07), 130 (30.68).

Anal. Calcd for $C_{17}H_{15}N_5O_4 \cdot {}^1/_2(C_4H_8O)$: C, 58.61; H, 4.92. Found: C, 58.75; H, 5.07.

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Registry No.—**1**, 120-72-9; **2**, 948-65-2; **3**, 487-89-8; **4**, 25365-71-3; **5**, 83-34-1; **6**, 91-55-4; **8**, 31951-33-4; **9**, 5257-24-9; **10**, 5257-06-7; **11**, 41601-98-3; **12**, 41601-99-4; **13**, 41602-00-0.

Effect of *p*-Methoxybenzonitrile on the Course of the Stoichiometric Hydroformylation of Cyclopentene

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The presence of a nitrile, *e.g.*, *p*-methoxybenzonitrile, in the stoichiometric hydroformylation can have a profound effect on both the product distribution and the rate of the reaction. The hydroformylation of cyclopentene under N_2 in the presence of excess $HCo(CO)_4$ produces 52% cyclopentane; the addition of nitrile reduces this to 3% and produces aldehyde almost exclusively. The presence of nitrile retards the rate of hydroformylation when the reaction is conducted under N_2 but accelerates it under CO. These effects are rationalized on the basis of the available concentration of $HCo(CO)_3$ under the various conditions investigated.

In an earlier publication[1] it was shown that, when the stoichiometric hydroformylation of olefins was carried out in the presence of nitriles, the yield of aldehyde was dramatically increased. Thus, under otherwise identical conditions, the addition of 2 mol of PhCN/mol of $HCo(CO)_4$ resulted in an increase of aldehyde yield from 44 to 90%. This high yield, obtained in the presence of a 20-fold excess of olefin, was unexpected because the formation of each mole of aldehyde requires 2 mol of $HCo(CO)_4$ and there were no suggestions in the literature that the final hydrogenolysis step was so fast relative to the earlier $HCo(CO)_4$-consuming steps. Because of these unusual results, we have investigated the nitrile effect more thoroughly and report herewith the results of such studies. Cyclopentene was chosen as a substrate because of its favorable rate of reaction and because double-bond migration does not affect either olefin or aldehyde composition.

Experimental Section

Toluene solutions of $HCo(CO)_4$ were prepared and analyzed according to established procedures.[2] Cyclopentane and cyclopentanecarboxaldehyde were obtained from cyclopentene (Phillips Research Grade) by known catalytic hydrogenation and hydroformylation procedures respectively. Glpc analyses were performed on a Pye Series 105, Model 15, gas chromatograph using a 7 ft × 0.25 in. glass column packed with 25% Carbowax on Chromosorb P. Peak areas were measured with a Disc integrator and were corrected for flame ionization detector response by the use of cyclohexane and mesitylene as internal standards. All reactions were performed at constant temperature (±0.1°) under a static atmosphere.

A typical reaction was conducted as follows. A toluene solution of $HCo(CO)_4$, which had been equilibrated at the desired reaction temperature under CO for 10 min, was syringed into a stirred toluene solution of cyclopentene, cyclohexane, mesitylene, and *p*-methoxybenzonitrile, which had been previously equilibrated under the desired reaction conditions for 10 min. To minimize initial concentration variations, sets of reactions were performed with aliquots from $HCo(CO)_4$ as well as olefin standard stock solutions. At appropriate intervals, 0.2-ml reaction mixture aliquots were withdrawn and quenched by addition to 0.2 ml of a 1.6 *M* toluene solution of triphenylphosphine; all cobalt carbonyl compounds precipitate as insoluble phosphine derivatives. The resulting, clear supernatant was then analyzed by glpc. [The reaction of triphenylphosphine with $HCo(CO)_4$ is extremely fast[3] and the resulting insoluble phosphine complex is unreactive as a hydroformylation catalyst under these conditions.[4]]

Results

Most studies on the stoichiometric hydroformylation have been carried out in the presence of excess olefin. We have followed this practice but, in addition, have also investigated reactions having $HCo(CO)_4$ in excess. The results of both studies are shown in Table I.

The first four reactions reported in Table I were performed in the presence of excess olefin. Reference to these results shows that, in the absence of nitrile, the rate of the reaction is more than 150-fold as fast under N_2 as under CO. Although this effect is well documented in the literature, its magnitude has not been previously defined. The presence of nitrile markedly slows the rate under N_2 but, surprisingly, accelerates it under CO. The yield of aldehyde in both instances is enhanced, as was expected from earlier work.[1]

Similar, but even more striking, results are obtained when the stoichiometric reaction is carried out with hydrocarbonyl in excess. In the absence of nitrile, the major product is cyclopentane regardless of the atmosphere employed. However, in the presence of nitrile, the major product is cyclopentanecarboxaldehyde; cyclopentane formation is negligible. The remarkable ability of *p*-methoxybenzonitrile to increase selectivity to aldehyde and to increase the rate of olefin consumption is brought out by the data shown in graphical form in Figure 1.

(1) L. Roos and M. Orchin, *J. Org. Chem.*, **31**, 3015 (1966).
(2) M. Orchin, *Advan. Catal.*, **16**, 1 (1966).
(3) R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 657 (1963).
(4) L. Roos, Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1965.