HOFMANN DEGRADATION OF 2,3-DIHYDRO-9-PHENYL-1H,9H-PYRAZOLO[1,2-a]INDAZOLE DERIVATIVES

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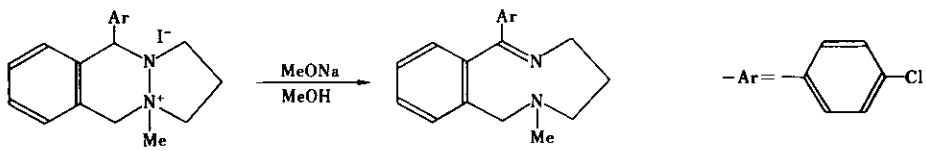
Abstract —— Treatment of 2,3-dihydro-9-phenyl-1H,9H-pyrazolo[1,2-a]indazoles (2) with alkyl iodides followed by heating with potassium hydroxide solution gave 1-alkyl-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocines (A) and 2-(3-alkylaminopropylamino)benzophenones (B) through the 4-alkyl and the 10-alkyl quaternary salts of 2, respectively.

Aeberli and Houlihan[1] reported that the N-N bond cleavaged products were obtainable in the Hofmann degradation[2] of bridgehead hydrazine rings, as exemplified below.

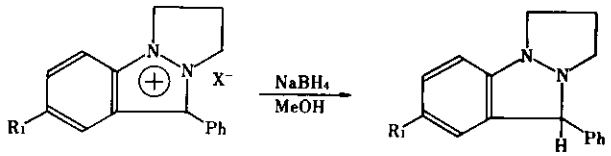


We previously prepared a number of 2,3-dihydro-1H-pyrazolo[1,2-a]indazolium salts (1) with an aim to develop drugs of bronchodilating activities.[3] The corresponding 9H-pyrazolo[1,2-a]indazole (2) readily obtainable from 1 is surely one of the desirable systems for the study of the Hofmann degradation of bridgehead hydrazine rings. We chose three 9-phenyl derivatives of 2 (2a, 2b and 2c) and investigated their alkylation with alkyl iodides and the reactions of the resulting quaternary salts with potassium hydroxide.

Reduction of 2,3-dihydro-7-methyl-9-phenyl-1H-pyrazolo[1,2-a]indazolium bromide (1b) with excess sodium borohydride in methanol gave 2,3-dihydro-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazole (2b) in 48% yield. The structure of 2b was established by analytical and spectral (MS and PMR) data (see experimental

section). In a similar manner, 2a and 2c were obtained from 1a and 1c, respectively (Table I).

Table I. 2,3-Dihydro-1H,9H-pyrazolo[1,2-a]indazoles

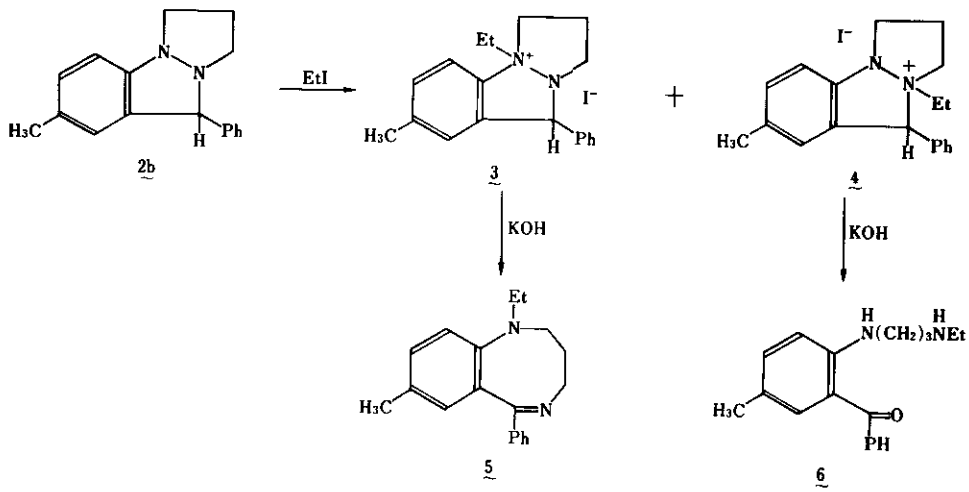


1 2

No	R_1	Yield (%)	mp (°C)
2a	H	60	73–74 (hexane)
2b	CH_3	48	79–80 (hexane)
2c	Cl	84	114 (MeOH)[4]

Treatment of 2b with ethyl iodide in refluxing acetone for 1 h gave a mixture of 2,3-dihydro-4-ethyl-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazolium iodide (3) and 2,3-dihydro-10-ethyl-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazolium iodide (4) with the former predominating. The complete separation of this mixture into 3 and 4 by means of silica gel chromatography was not successful, but the respective pure samples could be obtained by recrystallization from ethanol-ether of each of the separated two fractions. The 9-proton and the 9-carbon of 3 appeared as a singlet at δ 5.72 and as a doublet at δ 72.32, respectively, in the PMR and CMR spectra. On the other hand, the 9-carbon of 4 appeared as a doublet at δ 82.11 and the 9-proton signal could not be clearly characterized owing to overlapping with aromatic proton signals. The proton signals of 4 were shifted fairly downfield as compared with those of 3, indicating that 3 is the 4-ethyl derivative and 4 is the 10-ethyl one.[1] When the mixture of 3 and 4 obtained from the above-mentioned reaction was directly treated with potassium hydroxide solution in refluxing methanol for 1 h afforded 1-ethyl-8-methyl-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (5) and 2-(3-ethylaminopropylamino)-5-methylbenzophenone (6) in 65 and 19% yields, respectively. The structures of 5 and 6 were established by the elemental analyses and the spectral examinations (see experimental section). Further it was confirmed that each of the pure quaternary salts, 3 and 4, gave 5 and 6 as the respective sole product, on treatment with potassium hydroxide. Thus, it was disclosed that ethylation of 2b occurred at both the 4- and the

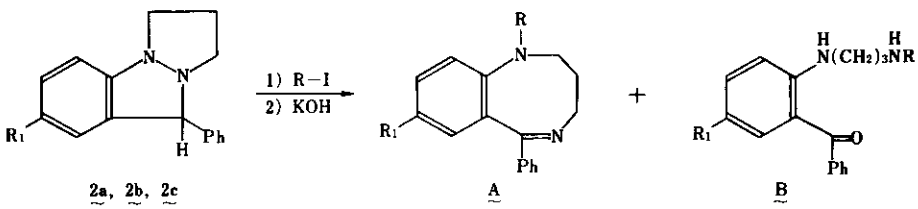
10-positions, and the 4-ethyl derivative 3 gave only the benzodiazocine 5 and the 10-ethyl derivative 4 produced only the aminobenzophenone 6.



2b 3 4 5 6

In a similar manner, 2a, 2b and 2c were alkylated with alkyl iodides, and the respective mixtures of quaternary salts were directly subjected to the Hofmann degradation with hot potassium hydroxide in methanol. In all cases, both the corresponding benzodiazocines (A) and aminobenzophenones (B) were obtained in fairly good yields (Table II).

Table II. Reactions of quaternary salts of 2a, 2b and 2c with KOH solution

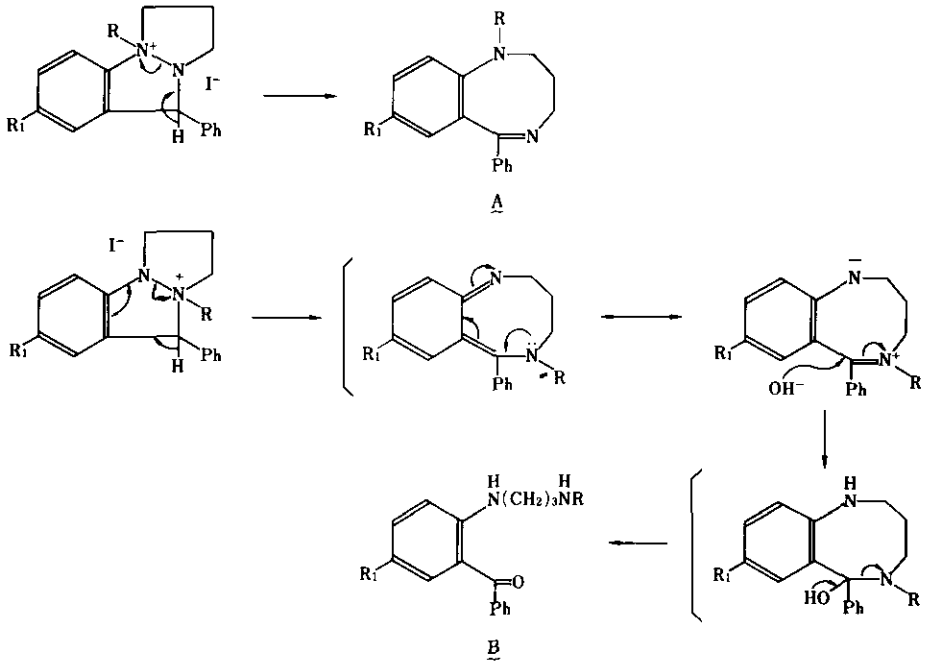


2a, 2b, 2c A B

			A		B		
Run	R_1	R	Yield (%)	mp (°C)[5]	Yield (%)	mp (°C)[7]	Ratio (A/B)
1	Cl	Me	28	118−119[6]	41	50[8]	0.68
2	"	nPr	60	73−75	27	220−222	2.22
3	Me	Me	52	73−74	39	203−205	1.33
4	"	Et	65	100−101	19	229	3.42
5	H	Me	47	120−122	48	198−200	0.98
6	"	Et	64	126−127	21	192−194	3.05

Amounts of A and B are directly proportional to those of the 4-alkyl and the 10-alkyl quaternary salts of 2, and the results shown in Table II indicate that

the ratio A/B is fairly affected by both the electronic and the steric factors. Apparently, alkylation at N_4 is accelerated by the increasing of the electron-density of N_4 (runs 1, 3 and 5). As for steric aspect, the alkylation at N_4 is more favorable than that at N_{10} independent of the nature or the 7-substituent R_1 (runs 1 and 2, 3 and 4, and 5 and 6). The formation of both A and B involves the elimination of the 9-proton. In the reaction of the 4-alkyl quaternary salts, the usual elimination of the β-proton and the fission of the N-N bond occurr to give benzodiazocines (A). On the other hand, in the reaction of the 10-alkyl quaternary salt, the aminobenzophenone (B) arises from the N-N bond fission and the elimination of the δ-hydrogen, that is, a conjugated Hofmann elimination. Products resulted from the fission of N_4-C_3 or N_{10}-C_1 bond were not detected at all.



A

B

EXPERIMENTAL

All melting points are uncorrected. NMR and CMR spectra were obtained on a Hitachi RB-24 spectrometer and a JEOL JUN-FX200, respectively, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 instrument. Infrared spectra were measured on a Hitachi 260-30 infrared spectrophotometer.

2,3-Dihydro-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazole (2b) —— A solution of 2,3-dihydro-7-methyl-9-phenyl-1H-pyrazolo[1,2-a]indazolium bromide (1b, 10 g) and $NaBH_4$ (4.5 g) in MeOH (200 ml) was stirred at room temperature for 1 h. The reactants were concentrated in vacuo and the residue was extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated in vacuo to give 3.65 g (48%) of 2b. An analytical sample, mp 79-80 °C, was prepared by recrystallization from hexane. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.56; H, 7.26; N, 11.25. MS m/z: 250(M^+). NMR ($CDCl_3$) δ: 1.80-2.37 (2H, m, H_2), 2.27 (3H, s, CH_3), 2.50-3.17 (2H, m, H_1 or H_3), 3,47 (2H, t, H_1 or H_3), 5.25 (1H, s, H_9), 6.5-7.4 (8H, m, Ar-H).

In a similar manner, 2a and 2c were obtained from 1a and 1c, respectively (Table I).

2,3-Dihydro-4-ethyl-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazolium iodide (3) and 2,3-Dihydro-10-ethyl-7-methyl-9-phenyl-1H,9H-pyrazolo[1,2-a]indazolium iodied (4) —— A mixture of 2b (10.14 g), EtI (9.36 g) and acetone (100 ml) was stirred under reflux for 1 h. The reaction mixture was cooled with ice and the precipitates were filtered to give a mixture (9.30 g) of 3 and 4. The mixture was chromatographed on silica gel with MeOH-$CHCl_3$ (0.03-0.1 : 1, V/V) to give 3 (6.40 g) and 4 (0.30 g), but they could not be separated completely.
An analytical sample of 3, mp 160-161°C, was prepared by recrystallization from EtOH-ether. Anal. Calcd for $C_{19}H_{23}IN_2$: C, 56.17; H, 5.71; N, 6.89. Found: C, 56.30; H, 5.63; N, 6.81. NMR ($CDCl_3$) δ: 1.30 (3H, t, $-CH_2\underline{CH}_3$), 2.38 (3H, s, $-CH_3$), 2.60-3.10 (2H, m, H_2), 3.68-5.06 (6H, overlapping multiplets, H_1, H_3, $\underline{CH}_2CH_3$), 5.72 (1H, s, H_9), 6.90-8.12 (8H, m, Ar-H). CMR ($CDCl_3$) δ: 9.89 (q), 21.42 (q), 27.52 (t), 51.81 (t), 62.13 (t), 70.18 (t), 72.32 (d), 117.78, 125.41, 128.52, 129.07, 131.33, 134.97, 137.21, 138.53, 142.50.
An analytical sample of 4, mp 174-175°C, was prepared by recrystallization from EtOH-ether. Anal. Calcd for $C_{19}H_{23}IN_2$: C, 56.17; H 5.71; N, 6.89. Found: C, 56.28; H, 5.74; N, 6.79. NMR ($CDCl_3$) δ: 1.28 (3H, t, $-CH_2\underline{CH}_3$), 2.32 (3H, s, $-CH_3$), 2.40-2.90 (2H, m, H_2), 3.14-4.80 (6H, overlapping multiplets, H_1, H_3, $-\underline{CH}_2CH_3$), 6.90-7.85(9H, m, Ar-H, H_9). CMR ($CDCl_3$) δ: 10.01

(q), 20.93 (q), 25.57 (t), 53.40 (t), 54.99 (t), 60.84 (t), 81.11 (d), 112.41, 125.29, 126.57, 129.38, 131.03, 131.39, 135.56, 143.78.

1,8-Dimethyl-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (5) and 2-(3-Ethylaminopropylamino)-5-methylbenzophenone (6) —— A mixture of 2b (2.50 g), EtI (2.34 g) and acetone (20 ml) was stirred under reflux for 1 h. Ether (25 ml) was added to the reactants to deposite precipitate which was filtered and washed with several portions of ether. The precipitate was dissolved in MeOH (20 ml) and KOH (2.5 g) in H_2O (10 ml) was added and the mixture was refluxed for 1 h. The reaction mixture was concentrated in vacuo and the residue was extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated in vacuo pressure. The residue was chromatographed on silica gel with $CHCl_3$ and 10% MeOH-$CHCl_3$ to give successively 5 (1.80 g, 65%) and 6 (0.55 g, 19%). An analytical sample of 5, mp 100-101°C, was prepared by recrystallization from hexane. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.71; H, 8.01; N, 9.95. IR(KBr) cm^{-1}: 1620 (-C=N). MS m/z: 278 (M^+). NMR ($CDCl_3$) δ: 1.19 (3H, t, $-CH_2\underline{CH}_3$), 1.50-1.95 (2H, m, H_3), 2.10 (3H, x, $-CH_3$), 2.90-4.08 (6H, overlapping multiplets, $-\underline{CH}_2CH_3$, H_2, H_4), 6.60-7.68 (8H, m, Ar-H). CMR ($CDCl_3$) δ: 12.82 (q), 19.93 (q), 22.49 (t), 46.45 (t), 47.34 (t), 49.69 (t), 114.39, 120.55, 124.40, 127.88, 129.04, 131.18, 132.91, 142.93, 147.41, 171.16 (s).

6 was a yellow oil. IR (neat) cm^{-1}: 1620 (-C=O). MS m/z: 296 (M^+). NMR ($CDCl_3$) δ: 1.10 (3H, t, $-CH_2\underline{CH}_3$), 1.20 (1H, br, $-CH_2\underline{NH}$-Et), 1.65-2.20 (2H, t, $-CH_2\underline{CH}_2CH_2$-), 2.13 (3H, s, $-CH_3$), 2.50-2.90 (4H, m, $-\underline{CH}_2NHCH_2$-), 3.15-3.45 (2H, m, Ph-$NHCH_2$-), 6.60-7.65 (8H, m, Ar-H), 8.40 (1H, br, Ph-NH-). CMR ($CDCl_3$) δ: 20.13 (q), 29.34 (t), 36.42 (q), 40.93 (t), 49.66 (t), 116.0 , 117.03, 122.40, 127.96, 128.87, 130.52, 134.98, 136.07, 140.65, 149.93, 199.05.

Product 6 was transformed to crystalline oxalate, mp 229°C (MeOH). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 64.97; H, 6.73; N, 7.21.

In a similar manner, 2a, 2b and 2c were successively treated with alkyl iodides and hot aq. KOH to give corresponding benzodiazocines (A) and aminobenzophenones (B) (Table II).

REFERENCES AND NOTES

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3) a) Y. Fujimura, S. Tanaka, I. Matsunaga, Y. Shiraki, Y. Ikeda, T. Yamazaki, Y. Ohba, S. Hata, M. Shindo, and K. Sakai, European patent No. 0023633 (1981);

b) Y. Shiraki and K. Sakai, Arch. Int. Pharmacodyn. Ther., 1983, 262, 150;

c) Y. Fujimura, Y. Shiraki, Y. Nawata, and I. Matsunaga, Yakugaku Zasshi in press.

4) 2c is an oily product which was transformed to the oxalte, mp 114°C (MeOH).

5) Recrystallized from hexane.

6) Lit.[9], mp 111-113°C. This compound was identified with the product synthesized according to the method of lit. 9 by comparison of their IR and NMR spectra.

7) Compounds (8) except those of R_1=Cl and R=Me, were oily products. They were transformed to oxalates and purified by recrystallization from MeOH.

8) Recrystallized from hexane.

9) M. E. Derieg, R. M. Schweininger and R. I. Fryer, J. Org. Chem., 1969, 34, 179.

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