Reactions of 2-Methyl-2*H*-cyclopenta[*d*]pyridazine with Benzenediazonium Tetrafluoroborate and *N*-Nitrosoacetanilide[1,2]

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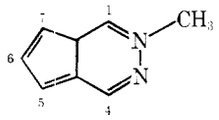
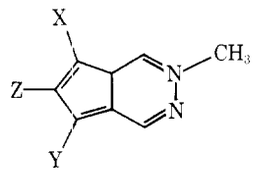
Reaction of 1 with 1 mol of $PhN_2^+BF_4^-$ in the presence of NaOAc gave the 5- (2) and 7-phenylazo derivatives (3) plus a little 5,7-diphenylazo product (4). Compound 4 was formed in high yield from 2 or 3. Reaction of 1 with excess $PhN_2^+BF_4^-$ and NaOAc or with excess *N*-nitrosoacetanilide gave 4 and the 5,7-diphenylazo-6-phenyl derivative (5). Compound 5 was also obtained from 4 and *N*-nitrosoacetanilide or, in lower yield, from 4 and PhN_2^+ BF_4^- in the absence of NaOAc. Reaction of the 5,7-dibromo derivative (6) with excess $PhN_2^+BF_4^-$ gave the corresponding 6-phenylazo compound (7), electrophilic displacement of the 7-Br group (9), and introduction of the 6-phenylazo group plus displacement of the 7-Br (8) or 5-Br (10) groups. The 5,7-diiodo derivative reacted similarly. The substituent long-wavelength shifts were found to be approximately additive except for the 6-phenylazo group.

Preceding papers showed that 2-methyl-2*H*-cyclopenta[*d*]pyridazine (1) undergoes electrophilic mono- and diacylation[5] and mono-, di-, and trihalogenation.[6] The 5- and 7-trifluoroacetyl compounds, in contrast to the corresponding azulene derivatives, underwent disubstitution readily. The reactions of 1, a π-excessive heteroanalogue of azulene, and several of its 5,7-disubstituted derivatives with benzenediazonium tetrafluoroborate and/or *N*-nitrosoacetanilide are now reported.



1

Reaction of 1 with 1.05 mol of benzenediazonium tetrafluoroborate in the presence of NaOAc readily formed the 5-phenylazo (2) and the 7-phenylazo (3) derivatives plus a small amount of the 5,7-diphenylazo compound (4). The ratio of 3 to 2 (2.5:1) corresponded approximately to those found previously for monoacylation[5] and monohalogenation[6] and provide additional evidence of the relative reactivity to electrophiles at the 5 and 7 positions. As for the acyl and halogen derivatives, the NMR chemical shift for H-4 was relatively larger than for H-1, J for the vicinal five-ring hydrogen coupling was smaller, and the NCH_3 was more deshielded for the 7-isomer (3). Treatment of 2 or 3 with 1 mol of the diazonium salt gave 4 in 100 or 82% yield, respectively. The formation of 4 under mild conditions (0 °C to room temperature) shows the high reactivity of the ring system despite the presence of the strong deactivating group (para σ = 0.64).



2, Y = PhN_2; X = Z = H
3, X = PhN_2; Y = Z = H
4, X = Y = PhN_2; Z = H
5, X = Y = PhN_2; Z = Ph
6, X = Y = Br; Z = H
7, X = Y = Br; Z = PhN_2
8, X = PhN_2; Y = Br; Z = H
9, X = Z = PhN_2; Y = Br
10, X = Br; Y = Z = PhN_2
11, X = Y = I; Z = H
12, X = PhN_2; Y = I; Z = H
13, X = Z = PhN_2; Y = I
14, X = I; Y = Z = PhN_2

The reaction of azulene with *N*-nitrosoacetanilide gives 1-phenylazoazulene and 1-phenylazulene.[7] It was of interest to see if 1 would exhibit this dichotomy of reactivity. Treatment of 1 with excess *N*-nitrosoacetanilide in benzene gave two products. The NMR spectrum of one (16%) showed a singlet at δ 8.2 which corresponded to those observed for H-6 in the previously characterized 5,7-bis(trifluoroacetyl), 5,7-dicarbomethoxy, and 5,7-diacetyl derivatives.[5] It possessed two phenylazo groups and was therefore assigned the structure of the expected 5,7-disubstitution product 4. The major product (45%) was somewhat unexpected. It had a phenyl substituent in addition to two phenylazo groups. The absence of NMR absorption for H-6 and the finding that the compound was formed (34%) from *N*-nitrosoacetanilide and 4 led to assignment of position 6 for the phenyl group (5). The yield of the latter reaction was markedly decreased to 5% when a tenfold excess of acrylonitrile was present. This result points to a radical mechanism for the phenylation.

The reaction of 1 with excess benzenediazonium tetrafluoroborate and NaOAc in MeOH–DMF also gave 5 (50%) and 4 (19%). The correspondence of the yields to those from the reaction with *N*-nitrosoacetanilide is suggestive of common intermediates. In the absence of NaOAc, reaction of 4 with the diazonium salt gave a decreased yield (9%) of 5. Thus, the major path for phenylation apparently involves acetate and is not an electron transfer from the aromatic ring to the diazonium ion.[8] In the presence of added acid (phenyl radical formation inhibited and 4 largely protonated), the yield of 5 was <1%, and 70% of 4 was recovered.

Heating 4 with an excess of phenylazotriphenylmethane in benzene gave only a trace of 5, and this reaction with 1 gave no phenyl substitution. Azulene also gave a lower yield of phenylation product with phenylazotriphenylmethane than with *N*-nitrosoacetanilide.[7]

The behavior of several other 5,7-disubstituted derivatives of 1 was explored. Reaction of the 5,7-dichloro derivative[6] with either benzenediazonium tetrafluoroborate or *N*-nitrosoacetanilide gave a complex mixture of products in trace amounts which were not further studied. A complex mixture was also obtained from the reaction of the dibromo derivative 6[6] with excess benzenediazonium ion but in amounts such that four products could be identified. The principal one (16.7%) was formed by the introduction of a phenylazo group, and the absence of the signal for H-6 indicated 7 to be the structure. This was the first example of phenylazo substitution at the 6 position. The second product (5.8%) contained a phenylazo group in place of one of the bromines (absorption in the H-6 region was still present), and the more reactive 7-position (to form 8) was considered the more probable for this electrophilic displacement. The ultraviolet and visible spectra of this product (8) were very similar to those of 3 (and dissimilar to those of 2), and, in keeping with other derivatives having a strongly electron-attracting group in the 7 position,[5,10] the NMR spectrum showed a relatively large (0.84 ppm) chemical-shift difference between H-1 and H-4. Analogous substi-

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tutions for groups other than hydrogen have been observed with azulene derivatives.[9] An attempt to isolate the isomeric 5-phenylazo-7-bromo compound, which would be expected to be formed in about one-third the amount of **8**, from the residual product mixture was not successful. Two isomeric products (4.6 and 1.7%) contained two phenylazo groups, one arising from the displacement of the 7- or 5-Br, respectively, and the other indicated to be at the 6 position by the absence of NMR absorption for this hydrogen. The ultraviolet and visible spectra of these compounds were similar to those of **3** and **2**, respectively. These data and the yield ratio (2.7:1) led to the assignments of structures **9** and **10**.

The reaction of the 5,7-diiodo derivative **11**[6] with 2 equiv of the diazonium salt also gave a complex product mixture, and it was possible to isolate only three compounds which were given structures **12** (7.4%), **13** (7.7%), and **14** (0.7%), corresponding to **8**, **9**, and **10**. As with the latter, comparisons of the ultraviolet, visible, and NMR spectra with those of **2** and **3**, as well as with those of **8–10**, were used in assigning the structures. The H-1, H-4 chemical-shift difference was 0.94 ppm for **12**. Spectral comparison was of particular importance for the unstable **14** for which an elementary analysis was not obtained. A possible alternative structure, the 5-phenylazo-7-iodo compound, was considered unlikely, since the wavelength of the strongest absorption band was at 413 nm, in the region (ca. 375–410 nm) found for **9**, **10**, and **13**, similar compounds which have two phenylazo groups, in contrast to the location of this band near 260 nm for **8** and **12** which have one phenylazo group.

The earlier studies[5,6] on electrophilic substitution products of **1** showed that halogen and trifluoroacetyl groups caused spectral shifts of the long-wavelength absorption which were qualitatively additive for substituents in the 5, 6, and 7 positions. The data for the phenylazo derivatives from the present study are given in Table I. While the results do not permit the direct calculation of many shift values, the shift additivity seems to hold approximately for the 5,7-di-N=NPh, 5-Br-7-N=NPh, and 5-I-7-N=NPh compounds, but not for those compounds containing a 6-N=NPh group. The presence of a 5- or 7-N=NPh group overshadows the presence of other groups [5-N=NPh (**2**), 7-Br-5,6-di-N=NPh (**10**), and 7-I-5,6-di-N=NPh (**14**), all absorb at 412 ± 1 nm, and 7-N=NPh (**3**), 5-Br-7-N=NPh (**8**), 5-Br-6,7-di-N=NPh (**9**), 5-I-7-N=NPh (**12**), and 5-I-6,7-di-N=N-Ph (**13**) all absorb at 471 ± 3 nm]. When both 5- and 7-N=NPh groups are present, the 7-N=NPh dominates [5,7-di-N=NPh (**4**) absorbs at 469 nm and 6-Ph-5,7-di-N=NPh (**5**) at 480 nm]. No reaction was observed between the 5,7-bis(trifluoroacetyl) compound[5] and *N*-nitrosoacetanilide or between the 5,7-dicarbomethoxy compound[5] and the benzenediazonium salt. Treatment of the diester with *N*-nitrosoacetanilide gave mostly recovered diester and a trace of red product which was not characterized.

Table I. Long-Wavelength Spectral Shifts for Phenylazo-Substituted 2-Methyl-2*H*-cyclopenta[*d*]pyridazines

Substituent	λ_{max}[a] (obsd)	$\Delta\lambda_{max}$[a]	λ_{max}[a,b] (calcd)
2-CH_3[c]	395		
5-N=NPh	412	17	
7-N=NPh	468	73	
5,7-di-N=NPh	469	74	485
6-Ph-5,7-di-N=NPh	480	85	
6-Ph[d]			406[d]
5,7-di-Br,6-N=NPh	476	81	
6-N=NPh[d]			451[e]
5-Br-7-N=NPh	473	78	(476)[f]
5-Br-6,7-di-N=NPh	470	75	(516)[f]
7-Br-5,6-di-N=NPh	411	16	(485)
5-I-7-N=NPh	474	79	(474)[g]
5-I-6,7-di-N=NPh	474	79	(530)[g]
7-I-5,6-N=NPh	413	18	(481)[h]
5,6-di-N=NPh[d]			394[i] (400)[j]
6,7-di-N=NPh[d]			(462)[f] (468)[h]

[a] Nanometers. [b] Calculated on basis of additivity of shifts. [c] Parent system. [d] Not known. Calculated from 6-Ph-5,7-di-N=NPh. [e] Calculated from 5,7-di-Br.[6] [f] From calculated shift for 5-Br.[6] [g] From calculated shift for 5-I.[6] [h] From calculated shift for 7-I.[6] [i] From 7-Br-5,6-di-N=NPh. [j] From 7-I-5,6-di-N=NPh.

Experimental Section

Melting points were taken on a Fisher or Kofler hot stage and are uncorrected. Ultraviolet and visible spectra were recorded on a Cary Model 14 spectrophotometer. NMR spectra were recorded in δ (ppm) on a Varian Model A-60, T-60, or DA-60-11 spectrometer with reference to tetramethylsilane. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer with reference to perfluorotributylamine. Elemental analyses were performed by Dr. A. Bernhardt, Elbach über Engelskirchern, Germany. Reaction solvents were dry unless obviously otherwise. Organic solutions of products were dried over $MgSO_4$ unless otherwise specified. Davison silica gel (200–325 mesh) was used for column chromatography. Silica gel G or Merck GF-254 was used for plate chromatography. The petroleum ether had bp 20–40 °C.

5-Phenylazo-, 7-Phenylazo-, and 5,7-Diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (2, 3, and 4) from 1. To a stirred solution of 157 mg (0.818 mmol) of benzenediazonium tetrafluoroborate in 4 mL of DMF at −65 °C was added dropwise a solution of 102 mg (0.773 mmol) of **1** and 63.3 mg (0.773 mmol) of dry NaOAc. After 45 min at −65 °C and after 40 min with the bath removed, the mixture was poured into H_2O and extracted with CH_2Cl_2. The residue from the combined, washed (saturated NaCl), dried extracts was chromatographed (column, 1:1 ethyl acetate–hexane).

Preparative plate chromatography of the first fraction (159 mg) (CH_2Cl_2) separated 142 mg of crude **3** from 4.2 mg of by-product, and further elution (MeOH–CH_2Cl_2) gave 10 mg of crude **4**. Crystallization of the **3** from CH_2Cl_2, plate chromatography (CH_2Cl_2), and recrystallization from CH_2Cl_2–hexane gave 57.1 mg (33%) of **3** as red needles, mp 116–118 °C. The analytical sample had mp 117.5–118 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 258 (19), 293 (11.7), 392 (15.2), and 468 nm (14.3); NMR (acetone) δ 4.31 (s, 3 H), 6.72 (d of d, 1 H, J = 4 and 1 Hz), 7.2–8.0 (m, 6 H), 8.61 (d, 1 H, J = 1 Hz), and 9.43 (br s, 1 H). The infrared spectrum was recorded. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.01; H, 5.62; N, 23.60.

Trituration of the crude **4** with ether and recrystallization from acetonitrile gave 3.7 mg (1.4%) of **4** as red needles, mp 222.5–223.5 °C, and otherwise (UV, vis, NMR) identical with an authentic sample.

Plate chromatography (CH_2Cl_2) of the second fraction (37.8 mg) separated 24.7 mg from more polar material, and rechromatography gave 22.8 mg (13%) of **2** as orange needles: mp 126–127 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 233 (12.9), 257 (16.8), 316 (10.8), and 412 nm (26); NMR (acetone) δ 4.15 (s, 3 H), 6.77 (d of d, 1 H, J = 4.5 and 1 Hz), 7.2–8.0 (m, 6 H), 8.77 (d, 1 H, J = 1 Hz), and 9.32 (br s, 1 H); MS m/e 236.106 (calcd 236.110). The infrared spectrum was recorded. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12. Found: C, 70.85; H, 5.28.

5,7-Diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (4) from 2 or 3. A. From 3. A solution of 15.1 mg (0.0786 mmol) of benzenediazonium tetrafluoroborate in 2 mL of methanol was added slowly to a cold (ice bath), stirred solution of 18 mg (0.0763 mmol) of **2** and 7.1 mg (0.087 mmol) of dry NaOAc in 0.25 mL of CH_2Cl_2 and 1 mL of methanol. The mixture was allowed to come to room temperature (90 min), the solvent was removed, and the residue was extracted into CH_2Cl_2. Addition of hexane and concentration gave 21.3 mg (82%) of **4**, mp 221.3–222.3 °C. The analytical sample (from acetonitrile) had mp 222.5–223 °C; UV λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 251 (12), 275 (sh, 7.92), 348 (21.5), and 469 nm (23); NMR (acetone) δ 4.44 (s, 3 H), 7.1–8.0 (m, 10 H), 8.2 (s, 1 H), 9.54 (d, 1 H, J = 1.2 Hz), and 9.77 (d, 1 H, J = 1.2 Hz); the infrared spectrum was recorded. Anal. Calcd for $C_{20}H_{16}N_6$: C, 70.57; H, 4.74; N, 24.69. Found: C, 70.59; H, 4.83; N, 24.94.

B. From 2. As described in A, except that a several molar excess of benzenediazonium tetrafluoroborate and NaOAc was used and final purification was effected by plate chromatography, from 3.2 mg (0.014 mmol) of **2** was obtained 4.7 mg (ca. 100%) of **4**, mp 216–221.5 °C, and otherwise (UV, vis, R_f) identical with the material from A.

Reaction of 1 with *N*-Nitrosoacetanilide. A mixture of 36.5 mg

(0.309 mmol) of 1 and 295.9 mg (1.8 mmol) of *N*-nitrosoacetanilide was dissolved in 10 mL of dry benzene. After 4 h the mixture was chromatographed (column, CH_2Cl_2). The first red band (50:1 $HCCl_3$–acetone) was rechromatographed (plate, 1:1 petroleum ether–CH_2Cl_2) and recrystallization of the red solid (H_2O–acetone) gave 9.9 mg (45%) of 5,7-diphenylazo-6-phenyl-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**5**) as red needles: mp 262–264 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 248 (sh, 18), 295 (18), 384 (41), and 480 nm (22); NMR (HOAc) δ 4.18 (s, 3 H), 6.88 (m, 10 H), 7.17 (br s, 5 H), 9.28 (s, 1 H), and 9.37 (s, 1 H). Anal. Calcd for $C_{26}H_{20}N_6$: C, 75.00; H, 4.82; N, 20.19. Found: C, 74.80; H, 4.97; N, 20.02.

The material from the second red band (20:1 $HCCl_3$–acetone) was rechromatographed (plate, 1:1 petroleum ether–CH_2Cl_2) five times. Plate rechromatography of the less polar of the two major bands (four times with 1:1 petroleum ether–CH_2Cl_2 and three times with 2:1 petroleum ether–CH_2Cl_2) and then recrystallization (H_2O–acetone) gave 29.2 mg of **5**. The material from the more polar band was separated (plate chromatograph, CH_2Cl_2) into two fractions. Trituration of the more polar material with ether gave 14.6 mg (15.5%) of **4**. Both **4** and **5** were identical (mp, UV, vis) with authentic samples.

Reaction of 1 with Excess Benzenediazonium Tetrafluoroborate. After 4 days, the red solution from the reaction of 31 mg (0.235 mmol) of **1**, 127 mg (1.55 mmol) of NaOAc in 4 mL of 1:1 DMF–MeOH with 310 mg (1.6 mmol) of benzenediazonium tetrafluoroborate was poured into 100 mL of H_2O and 75 mL of CH_2Cl_2, and the whole was shaken. Column chromatography (CH_2Cl_2) of the red oil from the washed (H_2O), dried CH_2Cl_2 layer and plate chromatography (1:4 petroleum ether–CH_2Cl_2) of the red solid obtained gave 48.6 mg (50%) of **5**, mp 260–262 °C, identical (UV, vis, R_f) with an authentic sample, and another red solid which, after trituration with ether, gave 11 mg of **4**, mp 219–221 °C. An additional 4.5 mg, mp 220–221 °C (total 15.5 mg, 19%), of **4** was obtained from the triturate. The material was identical (UV, vis, R_f) with an authentic sample.

Reaction of 4 with *N*-Nitrosoacetanilide. A. Absence of Inhibitor. After 6 h the solution from the reaction of 22.3 mg (0.0656 mmol) of **4** and 85.9 mg (0.522 mmol) of *N*-nitrosoacetanilide in 10 mL of dry benzene was chromatographed on silica gel (300:1 CH_2Cl_2–acetone). Plate chromatography (three times) of the material from the less polar band (1:1 CH_2Cl_2–petroleum ether) separated major (less polar) and minor bands from minor impurities. The major band gave 9.4 mg (34%) of **5**, mp 255–260 °C, and otherwise (UV, vis, R_f) identical with an authentic sample. The minor band contained 5.8 mg of unchanged **4**. Plate chromatobraphy (three times) of the material from the original more polar band (1:1 CH_2Cl_2–petroleum ether) afforded an additional 1.9 mg of **4**.

B. Plus Acrylonitrile. The reaction described in A was repeated with the addition of 0.5 mL (0.8 mmol) of dry acrylonitrile. The first eluent was 50:1 CH_2Cl_2–acetone. The more polar band from the plate chromatograph gave 1.4 mg (5.1%) of **5**, mp 262–265 °C, having UV and vis spectra identical with those of authentic material. The less polar band yielded 14.8 mg (66.4%) of unchanged **4**.

Reaction of 4 with Benzenediazonium Tetrafluoroborate. A. In DMF–MeOH. After 70 h, the solution from the reaction of 22.7 mg (0.0668 mmol) of **4** and 195 mg (1.01 mmol) of benzenediazonium tetrafluoroborate in 4 mL of 1:1 DMF–MeOH was poured into 75 mL of H_2O and 50 mL of CH_2Cl_2, and the whole was shaken. Plate chromatography (CH_2Cl_2) of the concentrate from the separated, washed (H_2O), dried, and filtered CH_2Cl_2 solution resolved three major bands. The least polar band gave 2.6 mg (9.4%) of **5**, mp 262–265 °C, and spectrally identical (UV, vis) with authentic material. The second band gave 0.8 mg of dark-purple needles: mp 210–240 °C (dec); UV λ_{max} (Et_2O) (D_{max}) 246 (sh, 0.36), 303 (0.38), 402 (0.68), and 499 nm (0.52) and not otherwise characterized. From the third band was obtained 12.4 mg (54.6%) of unchanged **4**.

B. In Acidic Methanol. A mixture of 26.7 mg (0.0785 mmol) of **4**, 325.4 mg (1.68 mmol) of benzenediazonium tetrafluoroborate, and 5 drops of concentrated HCl in 10 mL of MeOH was stirred for 70 h and then poured into 100 mL of CH_2Cl_2 and 75 mL of H_2O. The mixture was neutralized (K_2CO_3) and shaken. The aqueous phase was extracted with CH_2Cl_2, and the solvent was removed from the combined, washed (H_2O), dried, and filtered CH_2Cl_2 layers. Plate chromatography (CH_2Cl_2) of the residual red oil gave two main bands. Recrystallization (H_2O–acetone) of the material from the lesser yielded 0.3 mg (0.9%) of **5**, mp 263–266°C, and, similarly, the larger gave 18.6 mg (70%) of unchanged **4**.

Reaction of 5,7-Dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (6) with Benzenediazonium Tetrafluoroborate. After 3 h the solvent was removed from the reaction solution of 137.7 mg (0.474 mmol) of **6**[6] and 416.1 mg (2.17 mmol) of benzenediazonium tetrafluoroborate in 5 mL of CH_2Cl_2, 2 mL of DMF, and 2 mL of MeOH. Plate chromatography (twice, 1:1 petroleum ether–CH_2Cl_2) of the red residual oil gave four major bands with overlapping of the middle ones. Recrystallization (H_2O–acetone) of the solid from the least polar band gave 31.1 mg (17%) of 5,7-dibromo-6-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**7**) as red needles: mp 189–195 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 263 (sh, 16), 273 (18), 297 (sh 12), 312 (sh 11), 384 (11), and 476 nm (11); NMR (acetone) δ 4.4 (s, 3 H), 7.3–8.1 (two br m, 5 H), 8.83 (s 1 H), and 9.72 (s, 1 H). Anal. Calcd for $C_{14}H_{10}Br_2$: C, 42.64; H, 2.54; N, 14.21. Found: C, 42.86; H, 2.72; N, 14.41.

Rechromatography of the combined middle bands (CH_2Cl_2) resolved three major fractions. Recrystallization (H_2O–acetone) of the solid from the least polar band gave 9.1 mg (4.6%) of 5-bromo-6,7-diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**9**) as red needles, mp 189–193 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 249 (14), 283 (13), 371 (38), 454 (24), and 470 nm (24); NMR (acetone) δ 4.48 (s, 3 H), 7.3–8.2 (two br m, 10 H), 9.79 (s, 1 H), and 9.94 (s, 1 H). Anal. Calcd for $C_{20}H_{15}N_6Br$: C, 57.28; H, 3.58. Found: C, 57.50; H, 3.71. The second band was a mixture which was not characterized. Recrystallization (H_2O–acetone) of the solid from the most polar band gave 8.7 mg (5.8%) of 5-bromo-7-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**8**) as red needles: mp 147–148 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 259 (18), 297 (12), 391 (9.4), and 473 nm (9.4); NMR (acetone) δ 4.4 (s, 3 H), 8.1–7.25 (two br m, 6 H), 8.79 (s, 1 H), and 9.63 (s, 1 H). Anal. Calcd for $C_{14}H_{11}N_4Br$: C, 53.33; H, 3.49. Found: C, 53.44; H, 3.69.

Recrystallization (H_2O–acetone) of the solid from the fourth original band gave 3.3 mg (1.7%) of 5,6-diphenylazo-7-bromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**10**) as red needles: mp 164–167 °C; UV λ_{max} (Et_2O) (D_{max}) 240 (1.4), 255 (1.4), 312 (1.25), and 411 nm (1.97) with ϵ ca. 2×10^4. Anal. Calcd for $C_{20}H_{15}N_6Br$: C, 57.28; H, 3.58. Found: C, 57.69; H, 3.76.

Reaction of 5,7-Diiodo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (11) with Benzenediazonium Tetrafluoroborate. To the solution of **11** as obtained from the reaction of 87.6 mg (0.664 mmol) of **1** and 397.3 mg (1.75 mmol) of NIS in 15 mL of CH_2Cl_2,[6] was added 4 mL of 1:1 DMF–MeOH and 230 mg (1.2 mmol) of benzenediazonium tetrafluoroborate. After 2 h the red concentrate was chromatographed (plate, 1:1 CH_2Cl_2–petroleum ether). Rechromatography of the red solid obtained resolved a major, two minor, and several trace bands. The major, least polar band gave 101.5 mg of red crystals, mp 135–145 °C. Recrystallization from acetone separated 23.9 mg (7.7%) of 5-iodo-6,7-diphenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**13**) as red needles: mp 218–219 °C; UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 248 (14), 291 (14), 379 (36), 460 (21), and 474 nm (21); NMR (Me_2SO) δ 4.44 (s, 3 H), 8.2–7.3 (two br m, 10 H), 9.8 (s, 1 H), and 9.95 (s, 1 H). Anal. Calcd for $C_{20}H_{15}N_6I$: C, 51.50; H, 3.22. Found: C, 51.28; H, 3.38. Addition of H_2O to the filtrate and recrystallization of the precipitate from H_2O–acetone gave 33.4 mg of red needles which the NMR spectrum indicated to contain ca. 60% of **12**.

Recrystallization (H_2O–acetone) of the material from the second band gave 5.4 mg (2.3%) of 5-iodo-7-phenylazo-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**12**) as red needles, mp 171–173 °C. The second crop was 12.3 mg: mp 166–168 °C (total 17.7 mg, 7.4%); UV λ_{max} (Et_2O) ($\epsilon \times 10^{-3}$) 259 (14), 307 (12), 391 (8.8), and 474 nm (8.6); NMR (acetone) δ 4.46 (s, 3 H), 7.4–8.05 (two br m, 6 H), 8.7 (s, 1 H), and 9.64 (s, 1 H). Anal. Calcd for $C_{14}H_{11}N_4I$: C, 46.41; H, 3.04. Found: C, 46.25; H, 3.21.

Recrystallization (H_2O–acetone) of the solid from the third band gave 2.1 mg (0.7%) of red needles, mp 164–166 °C, tentatively characterized as **14** (spectral analogy to **10**): UV λ_{max} (Et_2O) (D_{max}) 233 (0.45), 250 (sh 0.41), 323 (0.4), and 413 nm (0.52).

Registry No.—**1**, 22291-85-6; **2**, 64414-29-5; **3**, 64414-28-4; **4**, 64414-27-3; **5**, 64414-26-2; **6**, 55268-20-7; **7**, 64414-25-1; **8**, 64414-24-0; **9**, 64414-23-9; **10**, 64414-22-8; **11**, 55268-23-0; **12**, 64414-21-7; **13**, 64414-20-6; **14**, 64414-19-3; benzenediazonium tetrafluoroborate, 369-57-3; *N*-nitrosoacetanilide, 938-81-8.

References and Notes

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(2) From the Ph.D. Thesis of L.D.G. (1970) and D.M.F. (1967), University of Washington.
(3) National Institutes of Health Fellow, 1968–1970.
(4) 3M Fellow, 1964–1965; National Science Foundation Summer Fellow, 1965.
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Relative Reactivity of Substituted 2-Alkoxy- and 2-Phenoxy-3,4-dihydro-2*H*-pyrans with *tert*-Butyl Hypochlorite. Effect of Substituents on Reactivity and Products[1]

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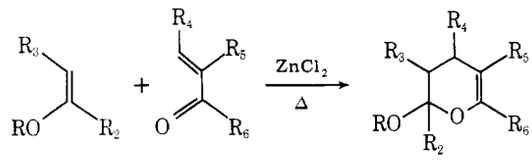
A series of substituted 3,4-dihydro-2*H*-pyrans were prepared: 2-methoxy- (**2a**), 2-methoxy-6-methyl- (**2b**), 2-methoxy-5-methyl- (**2c**), 2-methoxy-4-methyl- (**2d**), 2-methoxy-2-methyl- (**2e**), 2-methoxy-2,6-dimethyl- (**2f**), 2-ethoxy-3-methyl- (**2g**), 2-phenoxy- (**3a**), and 2-phenoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**). The structure of each 3,4-dihydro-2*H*-pyran was discussed in terms of configuration, where applicable, and preferred conformation. Generally, addition of *tert*-butyl hypochlorite to 3,4-dihydro-2*H*-pyrans yields 1,2-addition products. However, in the 2-alkoxy-3,4-dihydro-2*H*-pyran series, an alkyl group at either position C-2 or C-6 results in some 1,4-addition product, and alkyl groups at both positions yield 1,4-addition products exclusively. The effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring was determined using *tert*-butyl hypochlorite in competitive experiments with 3,4-dihydro-2*H*-pyran (**1**). The relative reactivities are **2f > 3b > 2b > 2d ≈ 2c > 1 > 2e > 2g > 2a ≈ 3a.**

Empirical observations in the course of our studies on the chemistry of 2-alkoxy-3,4-dihydro-2*H*-pyrans with various electrophilic reagents[2] has demonstrated an apparent dramatic effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring, as well as on the course or outcome of the reaction.[1] The object of this study was to synthesize a series of substituted 2-alkoxy- (**2a–g**) and 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**) and measure, in a relative sense with respect to 3,4-dihydro-2*H*-pyran (**1**), the effect of the substituent on both the reactivity of the 3,4-dihydro-2*H*-pyran ring system and product distribution using *tert*-butyl hypochlorite.

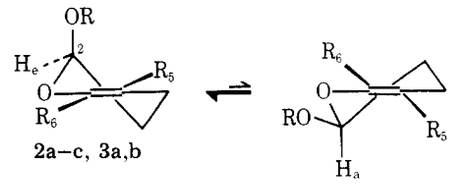
Synthesis and Structure. Substituted 2-alkoxy- and 2-phenoxy-3,4-dihydro-2*H*-pyrans generally are prepared by the thermally promoted cyclization[3] of appropriately substituted enol ethers and α,β-unsaturated aldehydes and ketones. We have found that the procedure[4] using various transition-metal salts as catalyst generally has an advantage over the thermally promoted cyclization, since both the temperature and reaction time for the cyclization can be drastically reduced. Because of this convenience, it is usually the method of choice even though the isolated yields for some of the substituted 3,4-dihydro-2*H*-pyrans are sometimes only moderate. Table I is a summary of the substituted 3,4-dihydro-2*H*-pyrans (**2a–g, 3a,b**) prepared by these procedures with the general reaction conditions and results.



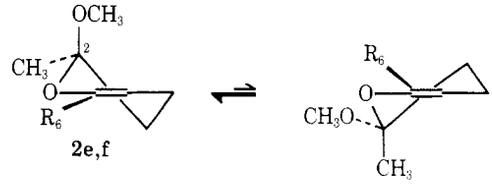
R = CH_3, CH_3CH_2, C_6H_5
R_{2-6} = H, CH_3

2a–g, 3a,b

The substituted 2-methoxy-3,4-dihydro-2*H*-pyrans **2a–c,** and the 2-phenoxy-3,4-dihydro-2*H*-pyrans **3a,b** all exist predominantly (ca. 80%, NMR analysis) in the conformation where the anomeric proton (H_e) is equatorial. The NMR signal for the anomeric C-2 proton at ca. δ 4.8 for the 2-methoxy-

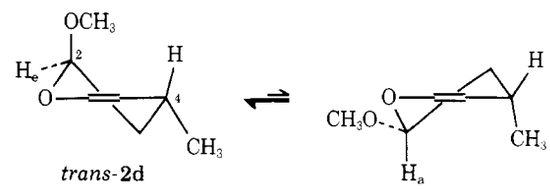


(**2a–c**) and at ca. δ 5.7 for the 2-phenoxy-3,4-dihydro-2*H*-pyrans (**3a,b**) is a superficial triplet ($J_{ea} \approx J_{ee} = \sim 3$ Hz) as expected for an equatorial proton at this position. This preference in the conformational equilibrium of 2-alkoxy-3,4-dihydro-2*H*-pyrans has been previously observed[5] and is predicted by the anomeric effect (Edward–Lemieux effect).[6] Since there is also only one conformer detected (NMR and GLC analysis) for the 2-methoxy-2-methyl-3,4-dihydro-2*H*-pyran (**2e**) and its 6-methyl derivative **2f** (no anomeric



proton in either), we assume the preferential conformation of these 3,4-dihydro-2*H*-pyrans to also have the C-2 methoxy group axial (anomeric effect), requiring the C-2 methyl to be in the favorable equatorial position.

In contrast, analysis (NMR and GLC) of 2-methoxy-4-methyl-3,4-dihydro-2*H*-pyran (**2d**) indicates a diastereomeric cis/trans mixture (60:40) at the anomeric C-2 carbon. The minor diastereomer *trans*-**2d,** derived from the exo approach



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