Remarkable Substituent Effects Found in the Base-catalyzed Reaction of 5-Methyl-2-(4′-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones

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Remarkable substituent effects found in the base-catalyzed reaction of 5-methyl-4-(1-methylethylidene)-2-(4′-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones (**2**) with acetone at reflux are described.

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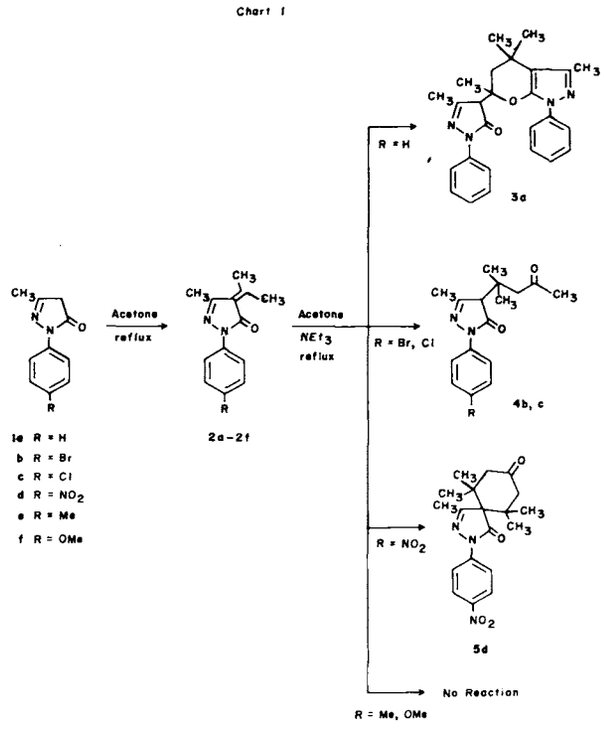
The tautomerism of 2,4-dihydro-3*H*-pyrazol-3-ones has been the most extensively studied in heterocycles and some review articles have been reported [1-4]. In these 2,4-dihydro-3*H*-pyrazol-3-ones, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one is especially examined because this is the mother skeleton of pyrine drugs such as antipyrine and aminopyrine and so on. Various 2-substituted phenyl derivatives have been synthesized and substituent effects on the predominant tautomer investigated. Through these studies, one group insisted on the relationship between 4′-substituents on the 2-phenyl group and the predominant tautomer [5], however, the other group strongly denied that conclusion [6]. Compared to these tautomeric studies from the viewpoint of physical chemistry, studies using these tautomeric 2,4-dihydro-3*H*-pyrazol-3-ones in organic synthesis have less been examined. We have been interested in utilizing these tautomerisms of 2,4-dihydro-3*H*-pyrazol-3-ones in organic synthesis and reported the facile ring transformation reaction [7] and the specific C_4-alkylation reaction [8]. In this manuscript, we wish to report the reaction of 5-methyl-2-(4′-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones **1** with acetone by a catalysis of triethylamine. Through these studies, we find the interesting fact that the reaction courses are governed by the substituents located remotely from the reaction sites.

Reaction of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**1a**) in acetone at reflux gives 5-methyl-4-(1-methylethylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**2a**) in nearly quantitative yield. Further reaction of **2a** in acetone containing triethylamine at reflux affords 3,4,4,6-tetramethyl-1-phenyl-6-(5′-methyl-2′-phenyl-2′,4′-dihydro-3*H*-pyrazol-3′-one-4′-yl)-1,4,5,6-tetrahydropyrano[2,3-*c*]-pyrazole (**3a**) in 70% yield. Under similar reaction conditions, reactions of **2b-2f** with acetone containing triethylamine are also examined, however, reaction products are different in these cases. From the reactions of **2b** and **2c**, one molar acetone adducts (**4b**, and **4c**) are obtained respectively, while from the reaction of **2d**, a two molar acetone adduct **5d** is obtained. In the case of **2e** and **2f**, no reaction occurred (only recovery of starting materials).

Chart I



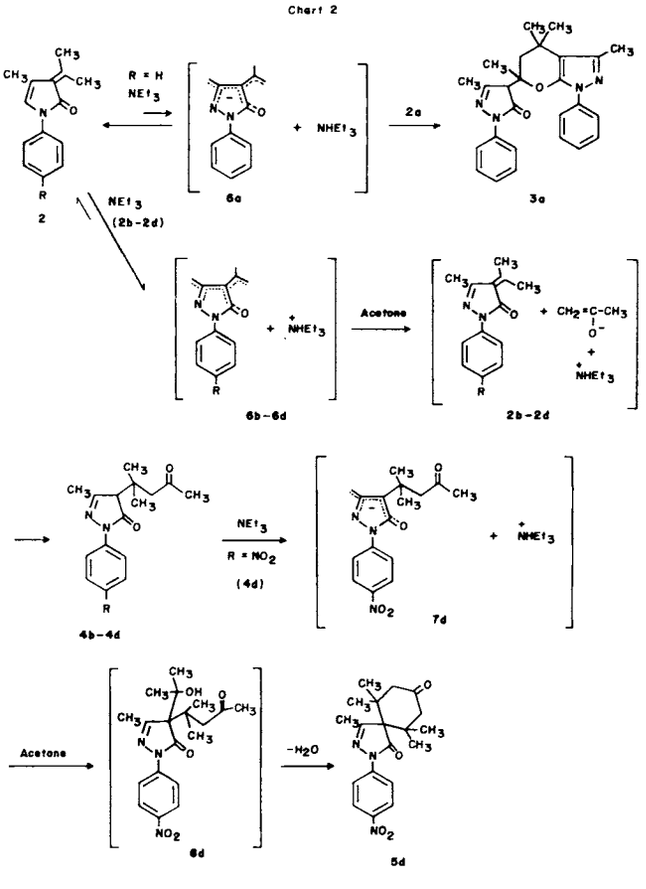
In the absence of triethylamine, **2a-2d** do not afford any final products such as **3a**, **4**, or **5d**. Thus the reactions to afford **3**, **4**, and **5** are considered to be the base-catalyzed reactions. In other words, the reactions are considered to be initiated with the deprotonation of **2**.

According to the results by Tutalkova *et al.* [9], the p*K*a values of 5-methyl-2-(4′-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones **1** are ordered as follows: 4′-OMe > 4′-Me > 4′-H > 4′-Br > 4′-Cl > 4′-NO_2. This order can be applied in these 5-methyl-4-(1-methylethylidene)-2-(4′-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones **2a-2f**. Owing to the large p*K*a values of 4′-Me (**2e**) and 4′-OMe (**2f**) derivatives, deprotonation of them by triethyamine does not occur (no reaction under the reaction conditions employed). The difference of the reaction products found in cases of **2a-2d** can be explained by considering the easiness of the deprotonation of **2a-2d** (acidity of **2a-2d**).

By triethylamine catalysis **2a-2d** are all deprotonated to afford the delocalized anions such as **6a-6d**. In the case of **2a**, the equilibrium (catalyzed by triethylamine) between **2a** and **6a** is shifted largely to the left side. In other words, owing to the large p*k*a value of **2a**, only a small portion of **2a** is deprotonated to afford the delocalized anion **6a**. The anion **6a** does not react with acetone but with the more reactive **2a** to give the dimer depicted as **3a**. In the cases of **2b-2d**, equilibria catalyzed by triethylamine are both shifted largely to the right side to afford the large amounts of delocalized anions **6b-6d**. In other words, small amounts of **2b-2d** which are not catalyzed by triethylamine to give **6b-6d** are present in the reaction media. As for the formation of a dimeric product such as **3**, the reaction of **2** with **6** (1:1) is necessary. So in these runs (**2b-2d**), no dimeric product such as **3** is obtained because of the low concentrations of **2b-2d**. On the other hand, these delocalized anions **6d-6d** are strong enough to promote the equilibrium of acetone molecule. By this equilibrium enolized acetone and **2b-d** are produced and the former (enolized acetone) attacks the enone moieties of **2b-2d** to give the one molar acetone adducts **4b-4d** respectively.

In the case of **4b** and **4c**, owing to their large p*k*a values, further reactions accompanying the deprotonations do not occur under the reaction conditions employed, however, in the case of **4d** which has a strong electron withdrawing substituent (NO_2), further reaction accompanying with the deprotonation of **4d** takes place.

Chart 2



The delocalized anion **7d** which is produced by the deprotonation of **4d** by triethylamine catalysis reacts smoothly with another mole of acetone to afford the acetone adduct **8d**. The two molar acetone adduct **8d** is dehydrated by the catalysis of triethylamine to afford the spiro compound **5d** as the final product.

It is well known that similar organic compounds react with reagents in like fashion. No such examples have been reported that remotely located substituents alter the reaction course. This manuscript is the first example to show that although producing common intermediates such at **6**, reaction products are different and are governed by delicate differences in p*k*a.

EXPERIMENTAL

All melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. The ir spectra were measured with a Jasco-A-3 spectrometer. The ^{1}H-nmr and ^{13}C-nmr (^{1}H-nmr 199.50 M Hz and ^{13}C-nmr 50.10 M Hz) were recorded with a Jeol JNM-FX-200 spectrometer using tetramethylsilane as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded with a Hitachi-MU-7MG spectrometer.

General Procedure for the Preparation of 5-Methyl-4-(1-methylethylidene)-2-(4'-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-ones **2a-2f**.

A solution of 5-methyl-2-(4-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**1**, 0.01 mole) in 300 ml of dry acetone was refluxed for 24 hours. The reaction mixture was evaporated *in vacuo* at room temperature leaving a dark brown solid, which was recrystallized from 2-propanol to afford 5-methyl-4-(1-methylethylidene)-2-(4'-substituted-phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2**) as yellow needles.

5-Methyl-4-(1-methylethylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**2a**).

This compound was obtained in 88% yield, mp 116-117°; ^{1}H-nmr (deuteriochloroform): δ 7.900-8.000 (m, 2H), 7.405-7.305 (m, 2H), 7.312-7.300 (m, 1H), 2.526 (s, 3H), 2.307 (s, 3H), 2.213 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 165.65 (s), 163.61 (s), 147.90 (s), 138.64 (s), 128.62 (d, 2C), 125.41 (s), 124.42 (d), 118.76 (d, 2C), 24.76 (q), 22.81 (q), 18.89 (q); ir (potassium bromide): 1685, 1620, 1588 cm^{-1}; ms: (m/e, relative intensity) 214 (M$^+$, 75), 199 (100).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.07; H, 6.74; N, 13.02.

5-Methyl-4-(1-methylethylidene)-2-(4'-bromophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2b**).

This compound was obtained in 86% yield, mp 158-159°; ^{1}H-nmr (deuteriochloroform): δ 7.860 (d, 2H, J = 9.0 Hz), 7.450 (d, 2H, J = 9.0 Hz), 2.538 (s, 3H), 2.322 (s, 3H), 2.271 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 166.41 (s), 163.54 (s), 148.31 (s), 137.70 (s), 131.60 (d, 2C), 125.27 (s), 120.12 (d, 2C), 117.15 (s), 24.86 (q), 22.94 (q), 18.88 (q); ir (potassium bromide): 1686, 1623, 1585 cm^{-1}; ms: (m/e, relative intensity) 294 (M$^+$, 95), 292 (M$^+$, 95), 279 (100), 277 (98).

Anal. Calcd. for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; N, 9.56; Br, 27.26. Found: C, 52.97; H, 4.79; N, 9.68; Br, 26.82.

5-Methyl-4-(1-methylethylidene)-2-(4'-chlorophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2c**).

This compound was obtained in 85% yield, mp 151-152°; ^{1}H-nmr

(deuteriochloroform): δ 7.915 (d, 2H, J = 8.8 Hz), 7.249 (d, 2H, J = 8.8 Hz), 2.527 (s, 3H), 2.307 (s, 3H), 2.249 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 166.50 (s), 163.44 (s), 148.24 (s), 137.10 (s), 129.24 (s), 128.58 (d, 2C), 125.10 (s), 119.58 (d, 2C), 24.84 (q), 22.87 (q), 18.90 (q); ir (potassium bromide): 1684, 1624, 1589 cm^{-1}; ms: (m/e, relative intensity) 250 (M$^+$, 35), 248 (M$^+$, 90), 235 (33), 233 (100).

Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26; Cl, 14.25. Found: C, 62.94; H, 5.41; N, 10.98; Cl, 14.52.

5-Methyl-4-(1-methylethylidene)-2-(4'-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2d**).

This compound was obtained in 87% yield, mp 210-212°; ^{1}H-nmr deuteriochloroform): δ 8.210 (s like, 4H), 2.621 (s, 3H), 2.433 (s, 3H), 2.399 (s, 3H); ^{13}C-nmr δ 167.80 (s), 164.10 (s), 149.67 (s), 143.73 (s), 143.60 (s), 125.00 (s), 124.68 (d, 2C), 117.69 (d, 2C), 25.05 (q), 23.25 (q), 18.98 (q); ir (potassium bromide): 1700, 1620, 1590 cm^{-1}; ms: (m/e, relative intensity) 259 (M$^+$, 70), 244 (100).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.53; H, 4,80; N, 16.45.

5-Methyl-4-(1-methylethylidene)-2-(4'-methylphenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2e**).

This compound was obtained in 83% yield, mp 182-184°; ^{1}H-nmr (deuteriochloroform): δ 7.800 (d, 2H, J = 8.8 Hz), 7.177 (d, 2H, J = 8.8 Hz), 2.586 (s, 3H), 2.375 (s, 3H), 2.329 (s, 3H), 2.311 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 165.22 (s), 163.56 (s), 147.65 (s), 136.22 (s), 134.15 (s), 129.21 (d, 2C), 125.66 (s), 119.07 (d, 2C), 24.79 (q), 22.84 (q), 20.90 (q), 18.95 (q); ir (potassium bromide): 1687, 1624, 1608 cm^{-1}; ms: (m/e, relative intensity) 228 (M$^+$, 85), 213 (100).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.07. Found: C, 73.93; H, 7.38; N, 11.85.

5-Methyl-4-(1-methylethylidene)-2-(4'-methoxyphenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2f**).

This compound was obtained in 80% yield, mp 170-172°; ^{1}H-nmr (deuteriochloroform): δ 7.790 (d, 2H, J = 9.3 Hz), 6.913 (d, 2H, J = 9.3 Hz), 3.798 (s, 3H), 2.592 (s, 3H), 2.379 (s, 3H), 2.324 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 165.43 (s), 163.39 (s), 156.87 (s), 147.58 (s), 132.06 (s), 125.57 (s), 120.85 (d, 2C), 114.01 (d, 2C), 55.53 (q), 24.81 (q), 22.84 (q), 18.95 (q); ir (potassium bromide): 1680, 1630, 1580 cm^{-1}; ms: (m/e, relative intensity) 244 (M$^+$, 100), 229 (85).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.18; H, 6.49; N, 11.31.

Reaction of **2a** with Acetone in the Presence of Triethylamine.

A solution of **2a** (4.28 g, 0.02 mole) in 300 ml of dry acetone containing triethylamine (20.20 g, 0.2 mole) was refluxed for 24 hours. After the reaction, the reaction mixture was evaporated *in vacuo* at room temperature to leave a dark brown oily residue, which was chromatographed on silica gel (60-230 mesh) using benzene as an eluent. From the first fraction 3,4,4,6-tetramethyl-1-phenyl-6-(5'-methyl-2'-phenyl-2',4'-dihydro-3*H*-pyrazol-3-one-4'-yl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole (**3a**, 3.25 g) was obtained as a white powder which was recrystallized from benzene to give analytically pure **3a** (3.02 g, 70%) as white needles. Compound **3a** had mp 160-162°; ^{1}H-nmr (deuteriochloroform): δ 7.856-7.170 (m, 10H), 3.815 (s, 1H), 2.729 (d, 1H, J = 14.65 Hz), 2.363 (s, 3H), 1.851 (s, 3H), 1.785 (d, 1H, J = 14.65 Hz), 1.487 (s, 3H), 1.389 (s, 3H), 1.334 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 169.59 (s), 158.06 (s), 146.73 (s), 146.41 (s), 138.52 (s), 137.91 (s), 128.89 (d, 2C), 128.80 (d, 2C), 126.00 (d), 125.30 (d), 121.59 (d, 2C), 119.14 (d, 2C), 104.80 (s), 82.90 (s), 56.85 (d), 45.26 (t), 31.16 (q), 29.75 (q), 28.85 (s), 23.01 (q), 18.28 (q), 14.57 (q); ir (potassium bromide): 3060, 2970, 1780, 1615, 1595, 1580, 1520, 1195 cm^{-1}; ms: (m/e, relative intensity) 428 (M$^+$, 18), 215 (100), 199 (60).

Anal. Calcd. for $C_{26}H_{28}N_4O_2$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.05; H, 6.80; N, 12.83.

Reaction of **2b** with Acetone in the Presence of Triethylamine.

A solution of **2b** (5.86 g, 0.02 mole) in 300 ml of dry acetone containing triethylamine (20.20 g, 0.02 mole) was refluxed for 24 hours. After the reaction the reaction mixture was evaporated *in vacuo* at room temperature to leave a dark brown solid, which was recrystallized from 2-propanol to afford 5-methyl-4-(1'-methyl-4-oxopenta-2-yl)-2-(4''-bromophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**4b**, 5.67 g, 80%) as white needles. Compound **4b** had mp 140-141°; ^{1}H-nmr (deuteriochloroform): δ 7.781 (d, 2H, J = 9.0 Hz), 7.472 (d, 2H, J = 9.0 Hz), 4.025 (s, 1H), 3.389 (d, 1H, J = 18.3 Hz), 2.259 (s, 3H), 2.310 (d, 1H, J = 18.3 Hz), 2.200 (s, 3H), 1.339 (s, 3H), 0.896 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 207.61 (s), 172.34 (s), 159.11 (s), 137.21 (s), 131.78 (d, 2C), 120.42 (d, 2C), 117.76 (s), 57.87 (d), 51.68 (t), 35.62 (s), 31.04 (q), 27.36 (q), 25.40 (q), 19.21 (q); ir (potassium bromide): 2960, 2940, 1600, 1580 cm^{-1}; ms: (m/e, relative intensity) 352 (M$^+$, 22), 350 (M$^+$, 22), 294 (100), 292 (90).

Anal. Calcd. for $C_{16}H_{19}BrN_2O_2$: C, 54.71; H, 5.45; N, 7.98; Br, 22.75. Found: C, 55.09; H, 5.84; N, 8.30; Br, 22.32.

From the same procedure 5-methyl-4-(1'-methyl-4'-oxopenta-2'-yl)-2-(4''-chlorophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**4c**, 77%) was obtained as white needles. Compound **4c** had mp 132-134°C; ^{1}H-nmr (deuteriochloroform): δ 7.825 (d, 2H, J = 9.0 Hz), 7.813 (d, 2H, J = 9.0 Hz), 3.991 (s, 1H), 3.356 (d, 1H, J = 18.3 Hz), 2.308 (d, 1H, J = 18.3 Hz), 2.240 (s, 3H), 2.182 (s, 3H), 1.378 (s, 3H), 0.890 (s, 3H);^{13}C-nmr (deuteriochloroform): δ 207.58 (s), 172.25 (s), 159.08 (s), 136.71 (s), 129.97 (s), 128.77 (d, 2C), 120.07 (d, 2C), 57.82 (d), 51.60 (t), 35.57 (s), 31.01 (q), 27.27 (q), 25.35 (q), 19.16 (q); ir (potassium bromide): 2960, 2930, 1605, 1585 cm^{-1}; ms: (m/e, relative intensity) 308 (M$^+$, 14), 306 (M$^+$, 38), 250 (60), 248 (100).

Anal. Calcd. for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13; Cl, 11.56. Found: C, 62.85; H, 6.03; N, 9.46; Cl, 11.27.

Reaction of **2d** with Acetone in the Presence of Triethylamine.

A solution of 5-methyl-4-(1-methylethylidene)-2-(4'-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**2d**, 5.18 g, 0.02 mole) in 300 ml of dry acetone containing 0.2 mole of triethylamine was refluxed for 24 hours. After the reaction the reaction mixture was evaporated *in vacuo* at room temperature to leave a dark brown solid, which was chromatographed on silica gel using benzene as an eluent. From the first fraction **5d** was obtained as a yellow powder which was recrystallized from acetone to afford analytically pure **5d** as yellow prisms (4.48 g, 63%). Compound **5d** had mp 193-195°; ^{1}H-nmr (deuteriochloroform): δ 8.230 (s like, 4H), 3.441 (d, 2H, J = 13.4 Hz), 2.458 (s, 3H), 2.053 (d, 2H, 13.4 Hz), 1.355 (s, 6H), 0.976 (s, 6H); ^{13}C-nmr (deuteriochloroform): δ 200.92 (s), 175.32 (s), 161.04 (s), 144.39 (s), 142.35 (s), 124.83 (d, 2C), 118.37 (d, 2C), 64.39 (s), 51.01 (t, 2C), 41.23 (s, 2C), 28.27 (q, 2C), 27.97 (q, 2C), 21.05 (q); ir (potassium bromide): 2970, 1705, 1700, 1595, 1520, 1500 cm^{-1}; ms: (m/e, relative intensity) 357 (M$^+$, 20), 301 (13), 259 (100), 244 (70).

Anal. Calcd. for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.76. Found: C, 64.11; H, 6.79; N, 12.08.

Under the same reaction conditions employed in the cases of **2a**-2d, reactions of **2e** and **2f** with acetone in the presence of triethylamine are also explained, however, any final products can not be detected at all (only the recovery of **2e** and **2f** respectively).

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