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CYCLODIENONES. 9. REACTION OF 4-HALO-2,4,6-TRI-TERT-BUTYL-2,5-CYCLOHEXADIEN-1-ONES WITH PYRAZOLES AND PREPARATION OF 1-(2-HYDROXYPHENYL)- AND 1-(4-HYDROXYPHENYL)PYRAZOLES[1]

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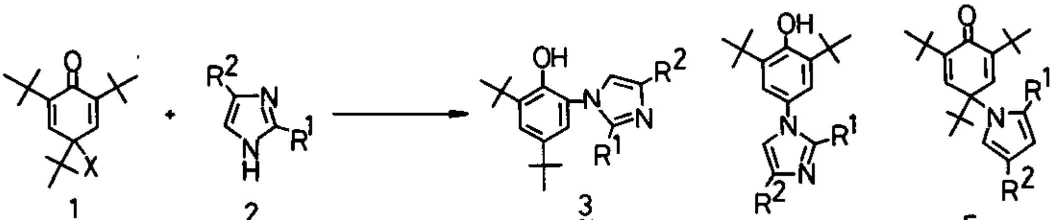
Abstract —— Reaction of 4-halo-2,4,6-tri-*tert*-butyl-2,5-cyclohexadien-1-one (**1**) with pyrazoles (**8**) afforded 4-(pyrazol-1-yl)-2,4,6-tri-*tert*-butyl-2,5-cyclohexadien-1-ones (**9**), 1-(4-hydroxy-3,5-di-*tert*-butylphenyl)- and 1-(2-hydroxy-3,5-di-*tert*-butylphenyl)pyrazoles (**10** and **11**) together with by-products. De-*tert*-butylation of **9**, **10** and **11** was carried out in boiling 85% H_3PO_4 to give the corresponding 1-(4-hydroxyphenyl)- and 1-(2-hydroxyphenyl)pyrazoles (**17** and **18**) in good yields, respectively.

Recently, we reported that reaction of 4-halo-2,4,6-tri-*tert*-butyl-2,5-cyclohexadien-1-ones (**1**) with imidazoles (**2**) afforded 1-(2-hydroxy-3,5-di-*tert*-butylphenyl)- and 1-(4-hydroxy-2,6-di-*tert*-butylphenyl)imidazoles (**3** and **4**) and 4-(imidazol-1-yl)-2,4,6-tri-*tert*-butyl-2,5-cyclohexadien-1-ones (**5**).[2]



1
a: X = Br
b: X = Cl

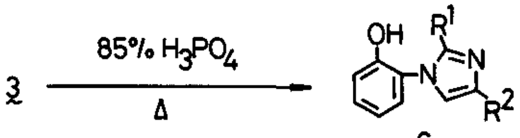
2

3

4

5

It was also found that these compounds 3, 4 and 5 were easily de-*tert*-butylated by treatment with boiling 85% H_3PO_4 to give the corresponding 1-(2-hydroxyphenyl)- and 1-(4-hydroxyphenyl)imidazoles (6 and 7) in almost quantitative yields, respectively.[3]



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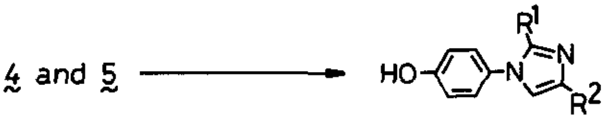

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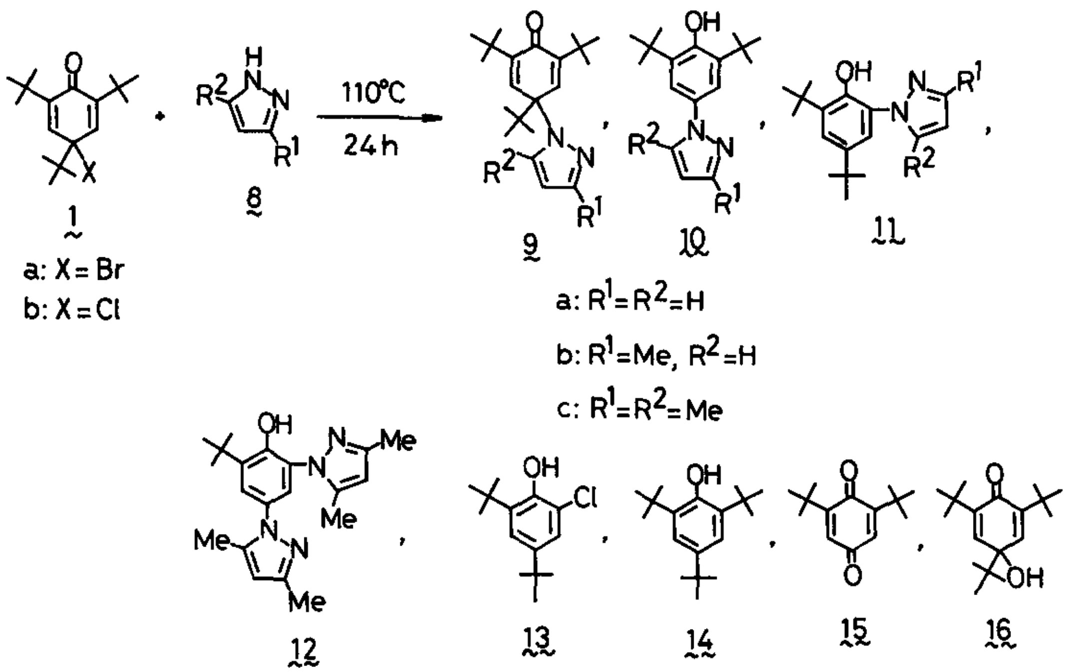
We now wish to report the reaction of 1 with pyrazoles (8) and de-*tert*-butylation of the reaction products.

RESULTS AND DISCUSSION

Reaction of 1 with pyrazoles (8).- Reaction of 1 with pyrazole (8a), 3-methyl- and 3,5-dimethylpyrazole (8b and 8c) was carried out at 110°C for 24 h and the results are summarized in Table 1 and Scheme 1.

As is shown in Table 1, the reactions of 1a and 1b with pyrazole (8a) itself afforded 4-(pyrazol-1-yl)-2,4,6-tri-*tert*-butyl-2,5-cyclohexadien-1-one (9a), 1-(4-hydroxy-3,5-di-*tert*-butylphenyl)- and 1-(2-hydroxy-3,5-di-*tert*-butylphenyl)pyrazole (10a and 11a) together with by-products such as 13, 14, 15 and 16 which are known compounds.[2] However, reactivity of 1a to 8a seems to be less than that of 1b. Reaction of 1b with 8b gave 9b, 10b and 11b in moderate yields, respectively. On the contrary, the case with 8c afforded 9c, 10c, 11c and 12 in poor yields. It might be explained by steric hindrance of the methyl group at 5 position of 8c. Compound 9 might be an intermediate for the formation of 10. Indeed when 9a was treated with hydrochloric acid in methanol, 10a was obtained in good yield.

$$\mathbf{9a} \xrightarrow[\text{MeOH}]{\text{HCl}} \underset{97\%}{\mathbf{10a}}$$



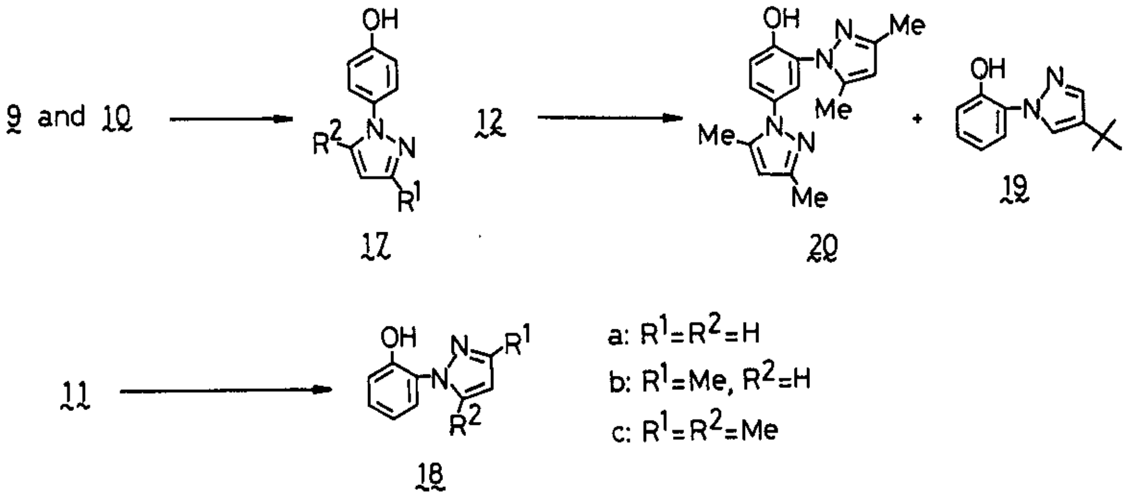
Scheme 1

Table 1. Reaction of 1 with 8 at 110°C (bath temperature) for 24h.a)

Run	Dienone	Pyrazole	Products (%)
1	1a	8a	9a(2), 10a(21), 11a(21), 14(49), 15(trace)
2	1b	8a	9a(22), 10a(16), 11a(27), 13(11), 14(3), 15(2)
3	1b	8b	9b(14), 10b(41), 11b(33), 13(5), 14(2), 15(trace)
4	1b	8c	9c(15), 10c(6), 11c(6), 12(7), 13(23), 14(19), 15(2), 16(4)

a) Molar ratio: 1/8 = 1 mole/2 mole. Reaction was carried out under nitrogen atmosphere.

b) Isolated yields are shown.



Scheme 2

Table 2. The *tert*-butylation of 9, 10, 11 and 12 in boiling H_3PO_4 solution.$^{a)}$

Run	Substrate	Time (h)	Products (%)$^{b)}$
1	9a	12	17a (91)
2	9b	4	17b (99)
3	9c	4	17c (85)
4	10a	12	17a (88)
5	10b	4	17b (99)
6	10c	4	17c (92)
7	11a	18	18a (58), 19 (13)
8	11a	36	18a (70), 19 (6)
9	11b	4	18b (85)
10	11c	4	18c (95)
11	12	4	20 (66)$^{c)}$

a) Reaction temperature: 180°C (bath temperature).

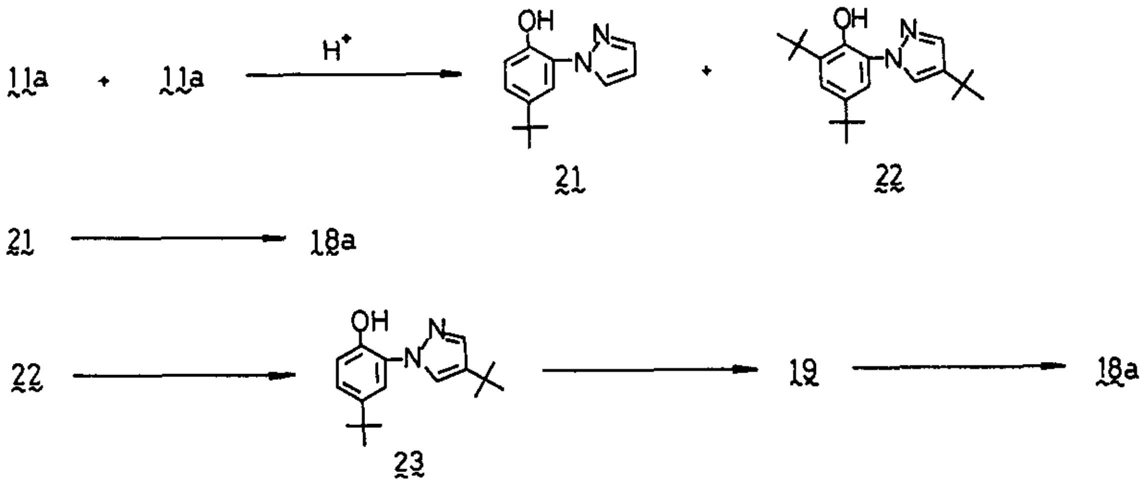
b) Isolated yields are shown.

c) Starting material 12 was recovered in 24% yield.

When the products 9, 10 and 11 were treated with boiling 85% H_3PO_4 according to the reported method,[3] the expected compounds were obtained in almost quantitative yields, respectively (Table 2 and Scheme 2).

It should be noted that prolonged reaction time was necessary to obtain 17a and 18a from 9a, 10a and 11a in high yield, respectively. The isolation of compound 19 in the de-*tert*-butylation of 11a might suggest that the dealkylation of *tert*-butyl group on the pyrazole ring occurred more slowly than that on the phenolic ring. Although the reaction pathway of formation of 19 is not clear, the following Scheme 3 might be tentatively proposed. Indeed, an intermediate 21 was obtained together with 19 and 18a when the reaction stopped after 4 h.

The reaction routes from 1 to 1-(2-hydroxy)- and 1-(4-hydroxyphenyl)pyrazoles seem to be a practical method.



Scheme 3

EXPERIMENTAL SECTION

Reaction of **1** with **8** (General Procedure).- After a mixture of **1** (5 mmol) and **8** (10 mmol) was heated at 110°C (bath temperature) for 24 h under nitrogen atmosphere, it was cooled to room temperature and poured into 50 ml of chloroform. The chloroform solution was washed with 30 ml of 10% hydrochloric acid, dried with sodium sulfate and evaporated in vacuo to leave the residue which was chromatographed on silica gel to afford the products (see Table 1).

Eluent solvent: hexane; products: **13**, **14**, **11**, **9** (eluent order): benzene; products: **16**, **15**, **10**, **12**.

9a: colorless prisms (MeOH-H_2O), mp 89-90°C, IR (KBr): $\nu_{C=O}$ 1665, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.97 (9H, s), 1.28 (19H, s), 6.25 (1H, dd, J = 2.2 and 2.0 Hz), 7.24 (2H, s), 7.48-7.57 (2H, m). Mass m/e (r.int): 328 (M^+, 38), 313 (58), 272 (100). Anal. Calcd for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.53. Found: C, 76.58; H, 9.70; N, 8.56.

9b: colorless plates (MeOH-H_2O), mp 69-71°C, IR (KBr): $\nu_{C=O}$ 1670, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.99 (9H, s), 1.27 (18H, s), 2.27 (3H, s), 6.00 and 7.88 (each 1H, d, J = 1.8 Hz), 7.20 (2H, s). Mass m/e (r.int): 342 (M^+, 2), 327 (6), 286 (100). Anal. Calcd for $C_{22}H_{34}N_2O$: C, 77.15; H, 10.00; N, 8.18. Found: C, 76.97; H, 9.96; N, 8.57.

9c: colorless prisms (MeOH-H_2O), mp 107-108°C, IR (KBr): $\nu_{C=O}$ 1665, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.20 (9H, s), 1.24 (18H, s), 2.12 and 2.20 (each 3H, s), 6.73 (1H, s), 6.88 (2H, s). Mass m/e (r.int): 356 (M^+, 3), 341 (5), 300 (100). Anal. Calcd for $C_{23}H_{36}N_2O$: C, 77.48; H, 10.18; N, 7.86. Found: C, 77.41; H, 10.11; N, 8.06.

10a: colorless prisms (C_6H_{14}), mp 132-133°C, IR (KBr): ν_{OH} 3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.48 (18H, s), 6.40 (1H, t, J = 2.0 Hz), 5.24 (1H, s, disappeared with D_2O), 7.66, 7.77 (each 1H, d, J = 2.0 Hz). Mass m/e (r.int): 272 (M^+, 100), 257 (99). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.94; H, 8.85; N, 10.36.

10b: colorless needles (C_6H_{14}), mp 127-128°C, IR (KBr): ν_{OH} 3100 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.46 (18H, s), 2.36 (3H, s), 5.19 (1H, s, disappeared with D_2O), 6.16, 7.62 (each 1H, d, J = 2.2 Hz), 7.34 (2H, s). Mass m/e (r.int): 286 (M^+, 100), 271 (76). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.55; H, 9.11; N, 9.59.

10c: colorless prisms (C_6H_{14}), mp 163-164°C, IR (KBr): ν_{OH} 3430 cm^{-1}. ^{1}H-NMR (CD-

Cl_3): δ 1.43 (18H, s), 2.21, 2.28 (each 3H, s), 5.25 (1H, s, disappeared with D_2O), 5.92 (1H, s), 7.12 (2H, s). Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 76.15; H, 9.44; N, 9.29.

11a: pale yellow liquid, IR (NaCl): ν_{OH} 3150 cm^{-1}, ^1H-NMR ($CDCl_3$): δ 1.32, 1.46 (each 9H, s), 6.44 (1H, t, J = 2.0 Hz), 7.17, 7.23 (each 1H, d, J = 2.2 Hz), 7.67, 7.91 (each 1H, d, J = 2.0 Hz), 11.16 (1H, s, disappeared with D_2O). Mass m/e (r.int): 272 (M^+, 43), 257 (100). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 75.04; H, 8.88; N, 10.28. Found: 74.96; H, 9.04; N, 10.00.

11b: colorless prisms (MeOH-H_2O), mp 43-45°C, IR (KBr): ν_{OH} 3100 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.31, 1.45 (each 9H, s), 2.36 (3H, s), 6.22 (1H, d, J = 2.2 Hz), 7.12, 7.18 (each 1H, d, J = 2.5 Hz), 7.80 (1H, d, J = 2.2 Hz), 11.42 (1H, s, disappeared with D_2O). Mass (r.int): m/e 286 (M^+, 50), 271 (100). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.33; H, 9.14; N, 9.54.

11c: colorless prisms (MeOH-H_2O), mp 110-111°C, IR (KBr): ν_{OH} 3450 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.28, 1.43 (each 9H, s), 2.28, 2.32 (each 3H, s), 6.00 (1H, s), 6.98, 7.23 (each 1H, d, J = 2.5 Hz), 9.49 (1H, s, disappeared with D_2O). Mass m/e (r.int) 300 (M^+, 69), 285 (100). Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 76.08; H, 9.38; N, 9.30.

12: colorless needles (C_6H_{14}), mp 181-183°C, IR (KBr): ν_{OH} 3450 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.44 (9H, s), 2.23, 2.28, 2.31, 2.37 (each 3H, s), 5.94, 6.02 (each 1H, s), 7.06, 7.24 (each 1H, d, J = 2.5 Hz), 10.04 (1H, br.s. disappeared with D_2O). Mass m/e (r.int): 338 (M^+, 100), 323 (52), 296 (62). Anal. Calcd for $C_{20}H_{26}N_4O$: C, 70.98; H, 7.74; N, 16.55. Found: C, 71.41; H, 7.91; N, 16.11.

Treatment of **9a** with 10% hydrochloric acid in methanol.- After a solution of 300 mg (9.13 mmol) of **9a** and 4 ml of conc.HCl in 20 ml of MeOH was refluxed for 2 h, it was poured into 50 ml of water. The solution was neutralized with $NaHCO_3$ and extracted with chloroform (20 ml x 4). The extract was dried over Na_2SO_4 and evaporated in vacuo to give 241 mg (97%) of **10a**.

De-tert-butylation in Boiling 85% H_3PO_4 (Typical Procedure).- After a suspension of 500 mg of **9b** in 3 ml of 85% H_3PO_4 was refluxed for 4 h, it was poured into 100 ml of ice-water. The reaction mixture was neutralized with $NaHCO_3$ and extracted with chloroform (30 ml x 5). The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated in vacuo to leave the residue which was chromatographed with silica gel using $CHCl_3$ as an eluent to give 252 mg (99%) of **17b**.

17a: colorless needles (C_6H_{14}), mp 108-108.5°C. ^1H-NMR ($CDCl_3$): δ 6.41 (1H, t, J =

2.0 Hz), 6.94, 7.34 (each 2H, d, J = 9.0 Hz), 7.68, 7.72 (each 1H, d.d., J = 2.0 and 0.5 Hz), 7.80-7.96 (1H, br. disappeared with D_2O). Mass m/e (r.int): 160 (M^+, 64), 131 (60), 52 (71), 39 (100). Anal. Calcd for $C_9H_8N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.94; H, 8.85; N, 10.36.

17b: colorless prisms ($CHCl_3$), mp 203.5-205°C. ^{1}H-NMR ($CDCl_3$): δ 2.36 (3H, s), 6.18, 7.62 (each 1H, d, J = 2.2 Hz), 6.77, 7.37 (each 2H, d, J = 9.0 Hz), 7.48-8.40 (1H, br. disappeared with D_2O). Mass m/e (r.int): 174 (M^+, 100), 173 (23), 146 (13). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.80; N, 16.05.

17c: colorless needles (C_6H_6-C_6H_{14}), mp 137-138°C. ^{1}H-NMR ($CDCl_3$): δ 2.16, 2.28 (each 3H, s), 5.93 (1H, s), 6.56, 7.02 (each 2H, d, J = 9.0 Hz), 10.09 (1H, br.s., disappeared with D_2O). Mass m/e (r.int): 188 (M^+, 100), 159 (84). Anal. Calcd for $C_{11}H_{12}N_2O$: C. 70.19; H, 6.43; N, 14.88. Found: C, 70.43; H, 6.45; N, 14.89.

18a: pale yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 6.46 (1H, t, J = 2.5 Hz), 6.62-7.42 (4H, m), 7.64 (1H, d, J = 2.0 Hz), 7.95 (1H, d, J = 2.3 Hz), 10.60 (1H, br.s. disappeared with D_2O). Mass m/e (r.int): 160 (M^+, 100), 131 (74). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 66.93; H, 5.04; N, 16.90.

18b: pale yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 2.33 (3H, s), 6.20 (1H, d, J = 2.5 Hz), 6.70-7.32 (m, 4H), 7.81 (1H, d, J = 2.5 Hz), 8.0-8.8 (1H, br, disappeared with D_2O). Mass m/e (r.int): 174 (M^+, 100), 145 (68). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.81; H, 5.84; N, 15.84.

18c: colorless needles (C_6H_{14}), mp 135-136.5°C. ^{1}H-NMR ($CDCl_3$): δ 2.29, 2.39 (each 3H, s), 6.00 (1H, s), 6.78-7.27 (4H, m), 8.0-10.5 (1H, br, disappeared with D_2O)). Mass m/e (r.int): 188 (M^+, 80), 159 (100). Anal. Calcd for $C_{11}H_{11}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.36; N, 14.64.

19[4]: pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.30 (9H, s), 6.70-7.37 (4H, m), 7.56, 7.76 (each 1H, br s), 11.44 (1H, s, disappeared with D_2O). Mass m/e (r. int) 216 (M^+, 31), 201 (100),

20: colorless prisms (C_6H_6-C_6H_{14}), mp 88.5-90°C. ^{1}H-NMR ($CDCl_3$): δ 2.27, 2.29, 2.31, 2.43 (each 3H, s), 5.96, 6.02 (each 1H, s), 7.02-7.29 (3H, m), 10.18 (1H, br s, disappeared with D_2O). Mass m/e (r.int): 282 (M^+, 100), 239 (11), 175 (12). Anal. Calcd for $C_{16}H_{18}N_4O \cdot H_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.12; H, 6.77; N, 18.46.

21: pale yellow oil. ^{1}H-NMR (CDCl$_3$): δ 1.32 (9H, s), 6.47 (1H, t, J = 2.1 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.18 (1H, dd, J = 8.4 and 2.2 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.98 (1H, d, J = 2.3 Hz), 11.00 (1H, s, disappeared with D$_2$O). Mass m/e (r.int): 216 (M$^+$). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.02; H, 7.48; N, 12.35.

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4. Elemental analysis of **19** could not be carried out since its amount was very small and its purification was very difficult.

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