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1,4- and 1,7-Addition Reactions of 4-(Substituted benzylidene)-3,5-dimethylisopyrazoles[1)]

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Reactions of 4-(substituted benzylidene)-3,5-dimethylisopyrazoles (**1a**—**1c**) with acetic anhydride, hydrochloric acid in methanol, bromine in acetic acid, dimethyl sulfate, and acyl chlorides (acetyl chloride, benzoyl chloride, ethyl chloroformate, and *p*-toluenesulfonyl chloride) in pyridine gave 1,4-addition products (**2**—**10**) in fairly good yield. On the other hand, 4-(*o*-nitrobenzylidene)isopyrazole (**1a**) was converted to 5-chloro-3-(1-substituted 3,5-dimethylpyrazolyl)anthranils (**13**, **14**, and **15**) by treatment with acetyl chloride, benzoyl chloride, or ethyl chloroformate without pyridine.

Keywords——isopyrazole; pyrazole; 1,4-addition; 1,7-addition; betaine; anthranil

In contrast to pyrazole chemistry, the reactivity of isopyrazoles has not been investigated extensively. Recently we have reported the 1,4-addition reaction of 4-(*m*-nitrobenzylidene)-3,5-dimethylisopyrazole (**1b**)[3)] and the reaction of 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazole (**1a**) with acyl chlorides[4)] in brief communications. The present paper describes further reactions of isopyrazoles (**1a**—**1c**), which exist in a betaine form,[5)] with a full account of the previous communications.[3,4)]

Treatment of **1b** with excess acetic anhydride at 50° for 10 hr gave 1-acetyl-4-(α-acetoxy-*m*-nitrobenzyl)-3,5-dimethylpyrazole (**2b**) in 92% yield, whose structure was supported by its analytical and spectral data [IR ν_{max}^{KBr} cm^{-1}: 1735, 1730; NMR ($CDCl_3$) δ: 2.10 and 2.21 (each 3H, each s, C_3– and C_5–CH_3), 2.60 and 2.63 (each 3H, each s, $2\times COCH_3$); mass spectrum (MS) *m/e*: 331 (M^+)]. Similarly, reactions of **1a** and **1c** with acetic anhydride under the same condition gave the diacetates (**2a** and **2c**). Their analytical and spectral data are summarized in Table I.

Reaction of **1a** to **1c** with a catalytic amount of hydrochloric acid in methanol gave 4-(α-methoxybenzyl)-3,5-dimethylpyrazoles (**3a**—**3c**) in 85—90% yield. These are presumably obtained by 1,4-addition of hydrochloric acid to isopyrazoles, followed by substitution of the chloro group with methanol. Their analytical and spectral data are summarized in Table II.

Brominations of **1a** to **1c** in acetic acid with an equivalent amount of bromine at 35° gave a mixture of benzaldehyde derivatives (**4a**—**4c**) in 40—45% yield and 4-bromo-3,5-dimethylpyrazole[6)] (**5**) in 50—55% yield. The mechanism of the formation of aldehydes and bromopyrazole seemed to start with 1,4-addition of acetic acid to isopyrazoles, accompanied by bromination as shown in Chart 1.

It is interesting to note that treatment of **1b** in absolute toluene with dimethyl sulfate under reflux in less than 0.5 hr gave 4-(α-methoxy-*m*-nitrobenzyl)-1,3,5-trimethylpyrazole (**6**)

1) A part of this work was presented at the 25th Meeting of Kinki Local Meeting of the Pharmaceutical Society of Japan, Kobe, November 1975.
2) Location: *Kawai, 2-10-65, Matsubara, Osaka 580, Japan.*
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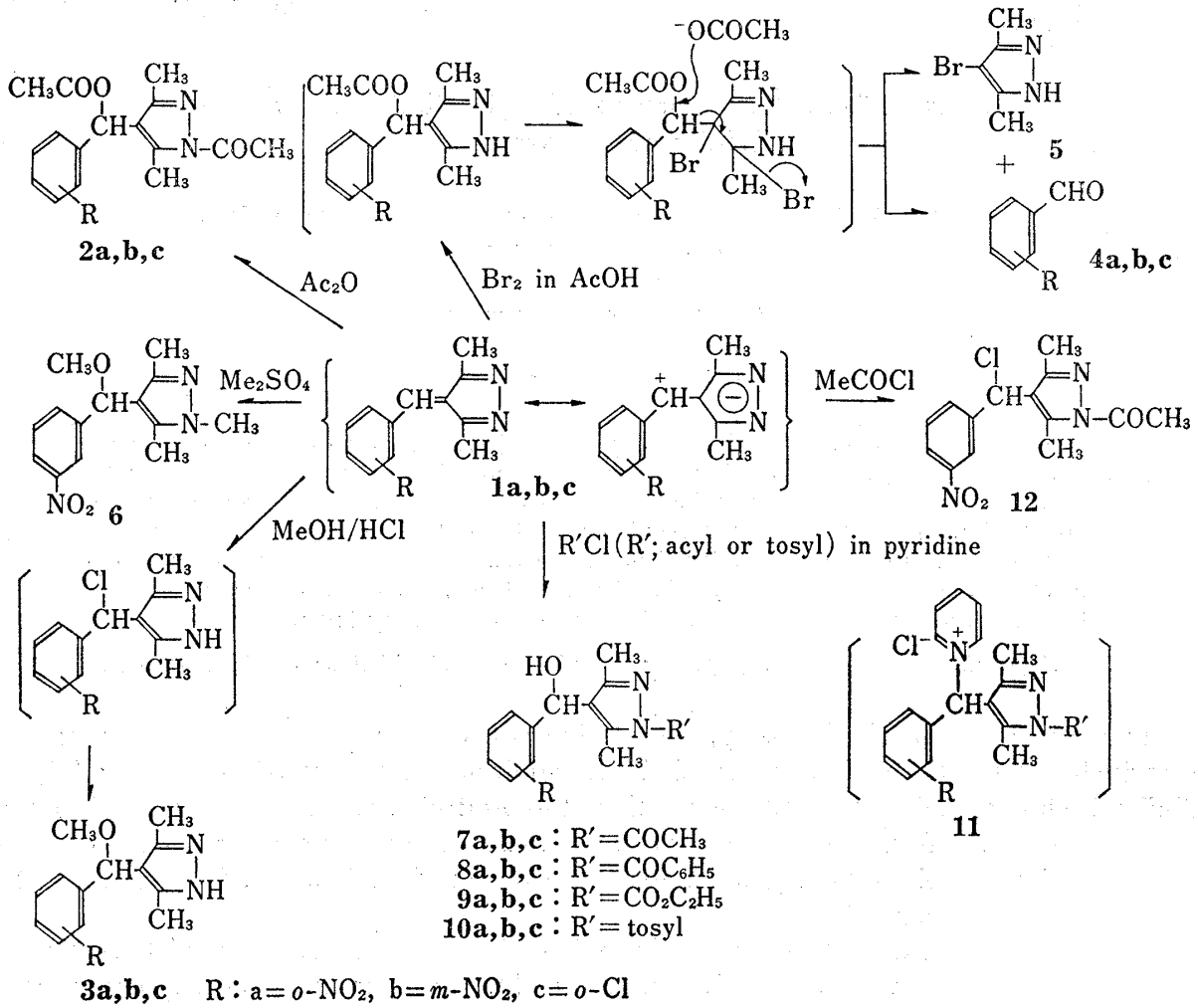
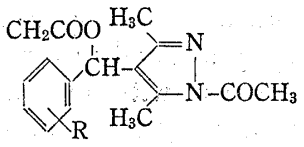


Chart 1

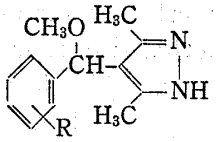
TABLE I. 1-Acetyl-4-(α-acetoxybenzyl)-3,5-dimethylpyrazoles



Compd. No.	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=O)	NMR ($CDCl_3$) δ -CH
2a	92	116—117(L)	$C_{16}H_{17}N_3O_5$	58.00 (58.28	5.32 5.17	12.68 12.72)	1735, 1730	7.60
2b	94	104—105(L)	$C_{16}H_{17}N_3O_5$	58.00 (58.30	5.32 5.42	12.68 12.68)	1735, 1730	6.95
2c	88	83— 84(PE)	$C_{16}H_{17}ClN_2O_3$	60.15 (59.90	5.42 5.34	8.62 8.74)	1730	7.05

Solvent: L=ligroin, PE=petroleum ether.

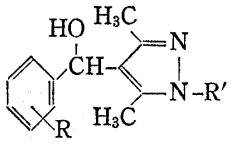
TABLE II. 4-(α-Methoxybenzyl)-3,5-dimethylpyrazoles



Compd. No.	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (NH)	NMR ($CDCl_3$) δ $-OCH_3$	$-CH$
3a	90	54— 55(L)	$C_{13}H_{15}N_3O_3$	59.75 (59.77	5.79 5.54	16.08 16.15)	3460	3.33	5.95
3b	86	139—140(L)	$C_{13}H_{15}N_3O_3$	59.75 (59.66	5.79 5.80	16.08 16.10)	3460	3.37	4.05
3c	90	112—113(PE)	$C_{13}H_{15}ClN_2O$	62.27 (62.14	6.03 6.14	11.17 11.30)	3460	3.37	5.50

Solvent: L=ligroin, PE=petroleum ether.

TABLE III. 1-Substituted 4-(α-Hydroxy)-3,5-dimethylpyrazoles



Compd. No.	R′	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (OH)	(C=O)	NMR ($CDCl_3$) δ $-CH$
7a	$COCH_3$	72	152—153 (B-L)	$C_{14}H_{15}N_3O_4$	58.12 (57.91	5.23 5.22	14.53 14.26)	3400	1740	6.45
7b	$COCH_3$	78	144—145 (M)	$C_{14}H_{15}N_3O_4$	58.12 (58.09	5.23 5.25	14.53 14.79)	3400	1740	5.95
7c	$COCH_3$	81	Oil[c]					3600[a]	1735[a]	6.05
8a	COC_6H_5	65	Oil[d]					3650[a]	1710[a]	6.45
8b	COC_6H_5	80	147—148 (B-PE)	$C_{19}H_{17}N_3O_4$	64.95 (65.22	4.88 4.87	11.96 11.98)	3400	1715	5.90
8c	COC_6H_5	75	Oil[c]					3650[a]	1710[a]	6.05
9a	$CO_2C_2H_5$	88	123—124 (B)	$C_{15}H_{17}N_3O_5$	56.42 (56.68	5.37 5.35	13.16 12.93)	3400	1760	6.45
9b	$CO_2C_2H_5$	72	114—115 (B-L)	$C_{15}H_{17}N_3O_5$	56.42 (56.67	5.37 5.17	13.16 13.33)	3350	1760	5.95
9c	$CO_2C_2H_5$	75	Oil[d]					3600	1755	6.15
10a	$SO_2C_6H_5CH_3$	65	171—172 (M)	$C_{19}H_{19}N_3O_5S$	56.86 (56.96	4.77 4.61	10.46 10.23)	3350	1380, 1190(SO_2)	6.15[b]
10b	$SO_2C_6H_5CH_3$	60	188—190 (M)	$C_{19}H_{19}N_3O_5S$	56.86 (56.64	4.77 4.49	10.46 10.49)	3350	1390, 1190(SO_2)	5.90[b]
10c	$SO_2C_6H_5CH_3$	58	153—154 (M)	$C_{19}H_{19}ClN_2O_3S$	58.38 (58.59	4.89 4.99	7.16 7.45)	3350	1395, 1190(SO_2)	5.75[b]

Solvent B=benzene, L=ligroin, M=methanol, PE=petroluem ether.

a) In $CHCl_3$ solution.

b) In DMSO-d_6.

c) **7c** and **8c** were analysed by leading to crystalline derivatives.

d) **8a** and **9c** failed to form crystalline derivatives, and these were determined by mass spectrum [**8a**: *m/e* 351 (M^+), **9c**: *m/e* 308 (M^+)].

in 25% yield, which was identified with an authentic sample[7] obtained by the reaction of *m*-nitrobenzylideneacetylacetone with methylhydrazine hydrochloride in methanol. However similar reactions of **1a** and **1c** with dimethyl sulfate failed.

Reaction of **1a** with a slight excess of acetyl chloride in pyridine at 50° for 10 hr, followed by treatment with ice-water gave 1-acetyl-4-(α-hydroxy-*o*-nitrobenzyl)-3,5-dimethylpyrazole (**7a**) in 72% yield, whose structure was determined by derivation to its diacetate (**2a**) by treatment with acetic anhydride. Similarly, reactions of **1a** to **1c** with acetyl chloride, benzoyl chloride, ethyl chloroformate, and *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine gave the corresponding 1-acetyl (**7b**, **7c**), 1-benzoyl (**8a**—**8c**), 1-ethoxycarbonyl (**9a**—**9c**), and 1-tosyl (**10a**—**10c**) derivatives, respectively, in a fairly good yield. Their analytical and spectral data are summarized in Table III.

Introduction of a hydroxyl group can be reasonably explained by postulating the pyridinium chloride (**11**) as an intermediate because 1-acetyl-4-(α-chlorobenzyl)-3,5-dimethylpyrazole (**12**) was isolated by treatment of **1b** with a large excess of acetyl chloride without pyridine.

On the other hand, reaction of **1a** with acetyl chloride without pyridine gave an entirely different result. Treatment of **1a** with a large excess of acetyl chloride at 50° for 10 hr resulted in isolation of crystalline **13** of mp 130—131° as a sole product, whose structure was assigned as 5-chloro-3-(1′-acetyl-3,5-dimethylpyrazolyl)anthranil from analytical and spectral data [IR ν_{max}^{KBr} cm^{-1}: 1740 (CO), no NO_2 group; UV λ_{max}^{EtOH} nm (log ε): 261 (3.86), 342 (4.06); NMR (DMSO-d_6) δ: 2.42 and 2.72 (each 3H, each s, $C\underline{H}_3$), 2.80 (3H, s, $COC\underline{H}_3$), 7.20—7.75 (3H, m, aromatic *H*)]. Hydrolysis of **13** with ethanolic sodium hydroxide gave 5-chloro-3-(3,5-dimethylpyrazolyl)anthranil (**16**) in a good yield.

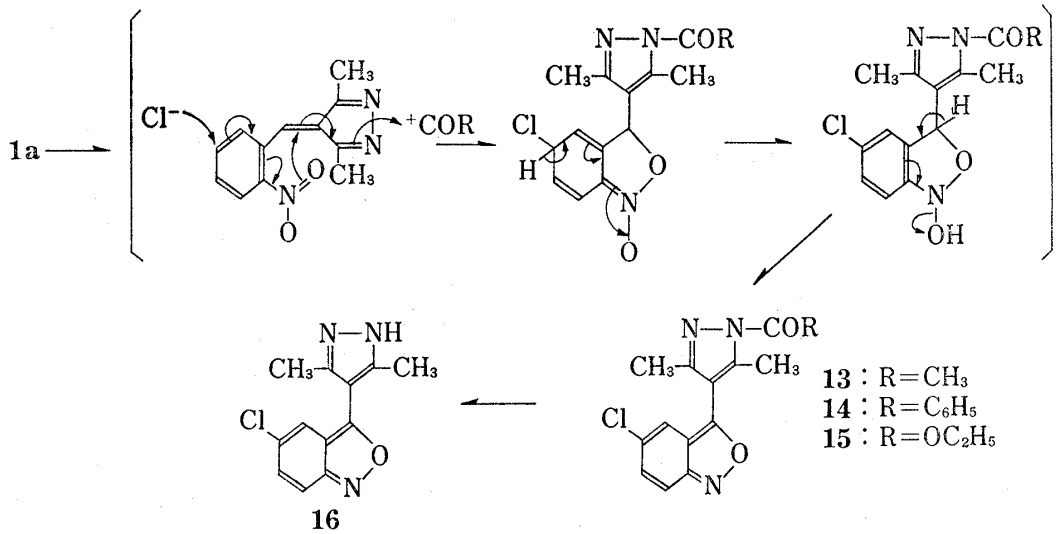


Chart 2

On the basis of the Dickenson's report[8] that *o*-nitrobenzhydrol cyclizes with introduction of a chlorine atom upon heating with thionyl chloride in chloroform to give 5-chloro-3-phenylanthranil, the mechanism of the formation of **13** was considered as the attack of nitro-oxygen on the benzyl-carbon of isopyrazole with the 1,7-addition of acetyl chloride, followed by prototropy and dehydration, resulting in the formation of the anthranil. Similarly, reaction of **1a** with benzoyl chloride and ethyl chloroformate gave 5-chloro-3-(1-benzoyl-3,5-dimethylpyrazolyl)anthranil (**14**) and 5-chloro-3-(1-ethoxycarbonyl-3,5-dimethylpyrazolyl) anthranil (**15**), respectively. Analytical and spectral data are summerized in Table IV.

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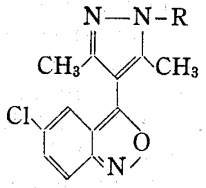
8) W.B. Dickenson, *J. Am. Chem. Soc.*, **86**, 3580 (1964).

TABLE IV. 5-Chloro-3-(1-substituted 3,5-dimethylpyrazolyl)anthranils



Compd. No.	R	Yield (%)	mp (°C) (Recryst. Solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=O)	UV λ_{max}^{EtOH} nm (log ε)
13	$COCH_3$	92	130—131 (MeOH)	$C_{14}H_{12}ClN_3O_2$	58.03 (58.33	4.17 4.36	14.50 14.39)	1740	261(3.86), 342(4.06)
14	COC_6H_5	58	155—156 (EtOH)	$C_{19}H_{14}ClN_3O_2$	64.86 (65.07	4.01 4.13	11.94 11.91)	1700	248(4.07), 342(4.07)
15	$CO_2C_2H_5$	87	103—104 (Petr. ether)	$C_{15}H_{14}ClN_3O_3$	56.36 (56.61	4.41 4.45	13.14 13.06)	1760	253(3.92), 337(4.00)

Experimental

Melting and sublimating points are uncorrected, Infrared (IR) spectra were determined on a JASCO Model IRA-1 and ultraviolet (UV) spectra on a Schimadzu UV-200 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined, using tetramethyl silane as the internal standard, with a Hitachi R-24A spectrometer, and mass spectra on a Hitachi RMU-7L.

1-Acetyl-4-(α-acetoxybenzyl)-3,5-dimethylpyrazoles (2a—2c)——A suspension of isopyrazoles (**1**) (0.01 mol) in Ac_2O (20 ml) was stirred at 50° for 10 hr. After decomposition of Ac_2O with saturated $NaHCO_3$ solution, the whole mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and the solvent was evaporated to afford a crystalline residue which was recrystallized from a suitable solvent to **2a**, **2b**, and **2c**.

4-(α-Methoxybenzyl)-3,5-dimethylpyrazoles (3a—3c)——A solution of **1** (0.01 mol) and 35% hydrochloric acid (0.5 ml) in MeOH (100 ml) was heated for 2 hr. After evaporation of the solvent, H_2O was added and the whole mixture was extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ solution and H_2O, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crystalline residue was recrystallized from a suitable solvent to **3a**, **3b**, and **3c**.

Bromination of Isopyrazoles (1a—1c)——To a solution of **1** (0.005 mol) in AcOH (25 ml), Br_2 (0.8 g) (0.005 mol), dissolved in AcOH (2 ml) was added in small portions under stirring at 35°. After stirring for 1 hr, AcOH was evaporated *in vacuo* and the viscous oily residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution and H_2O, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the pale yellow oily residue was submitted to an Al_2O_3 column chromatography using benzene as an eluant. From the first fraction were obtained benzaldehydes (**4a**, **4b**, and **4c**) in 40—45% yield, which were identified with each authentic sample by comparison of IR spectra. From the latter fractions was obtained 4-bromo-3,5-dimethylpyrazole (**5**) of mp 121—123° (lit.[6] 123°) recrystallized from hexane in 50—55% yield.

4-(α-Methoxy-*m*-nitrobenzyl)-1,3,5-trimethylpyrazole (6)——To a suspension of **1b** (1.15 g, 0.005 mol) in absolute toluene (30 ml) Me_2SO_4 (2.52 g, 0.01 mol) was added and the mixture was heated under reflux for 0.5 hr. The solvent was removed by concentration *in vacuo* and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% NH_4OH and H_2O, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the viscous oily residue was purified by column chromatography over an Al_2O_3. Elution with benzene gave **6** as colorless crystals (0.34 g) (25%). Sublimation at 130° (oil bath)/3 mmHg gave an analytical sample as colorless needles of mp 124—125°. NMR ($CDCl_3$) δ: 2.11 and 2.15 (each 3H, each s, C_3- and C_5-$C\underline{H}_3$), 3.38 (3H, s, $OC\underline{H}_3$), and 3.37 (3H, s, $NC\underline{H}_3$). MS *m/e*: 275 (M^+). *Anal.* Calcd. for $C_{14}H_{17}O_3N_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.09; H, 6.30; N, 14.92.

1-Substituted 4-(α-Hydroxybenzyl)-3,5-dimethylpyrazoles (7a—7c, 8a—8c, 9a—9c, and 10a—10c)——To a suspension of **1** (0.005 mol) in pyridine (10 ml) acetyl chloride, benzoyl chloride, ethyl chloroformate, or tosyl chloride (0.0055 mol) was added. The reaction mixture was stirred for 10 hr at 50—60°. After evaporation of pyridine *in vacuo*, the residue was triturated with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with cold 5% HCl and H_2O, and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the crystalline residue was recrystallized from a suitable solvent. The oily products were derived to crystalline derivatives and determined as described below.

Acetylation of **7c**: A solution of **7c** (278 mg, 1 mmol) in Ac_2O (5 ml) and pyridine (1 drop) was allowed to stand overnight at room temperature. The mixture was poured into ice-water, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crystalline residue was recrystallized from petr. ether to colorless needles (75 mg) of mp 112—113°. This was identified with the authentic sample of **2c**.

Benzoylation of **8c**: A solution of **8c** (1.7 g, 0.005 mol) in pyridine (10 ml) and BzCl (1.4 g, 0.01 mol) was stirred at 60° for 5 hr. After pyridine was evaporated *in vacuo*, H_2O was added and the whole mixture was extracted with $CHCl_3$. The solvent was evaporated and the crystalline residue was recrystallized from benzene-ligroin to 1-benzoyl-4-(α-benzoxy-*o*-chlorobenzyl)-3,5-dimethylpyrazole as colorless needles (0.85 g), mp 115—117°. IR ν_{max}^{KBr} cm^{-1}: 1717 and 1705. NMR ($CDCl_3$) δ: 2.20 (3H, s, C_3–C<u>H</u>$_3$), 2.75 (3H, s, C_5–C<u>H</u>$_3$). *Anal.* Calcd. for $C_{26}H_{21}ClN_2O_3$: C, 70.19; H, 4.76; N, 6.30. Found: C, 70.26; H, 4.77; N, 6.54.

1-Acetyl-4-(α-chloro-*m*-nitrobenzyl)-3,5-dimethylpyrazole (12)——To a suspension of **1b** (1.15 g, 0.005 mol) in MeCOCl (30 ml), a drop of pyridine was added and the mixture was heated under stirring at 50° for 10 hr. After evaporation of MeCOCl *in vacuo*, the residue was dissolved in $CHCl_3 \cdot CHCl_3$ solution was washed with H_2O and saturated $NaHCO_3$ solution, and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a clear viscous oil which showed one spot on thin-layer chromatography (Al_2O_3/benzene) and a positive Beilstein test. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: no OH, 1738 (CO). NMR ($CDCl_3$) δ: 2.05 and 2.55 (each 3H, each s, C_3- and C_5–C<u>H</u>$_3$), 2.65 (3H, s, COC<u>H</u>$_3$), and 6.20 (1H, s, C<u>H</u>). These data are in fair agreement with the structure of **12**. The oily compound **12** (1 g) dissolved in MeOH (20 ml) was refluxed for 1 hr. After evaporation of the solvent, the residue was dissolved in $CHCl_3 \cdot CHCl_3$ solution was washed with saturated $NaHCO_3$ solution and H_2O, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crystalline residue was recrystallized from ligroin to colorless needles (0.42 g) of mp 139—140° which was identified with the authentic sample of **3b**.

5-Chloro-3-(1-substituted 3,5-dimethylpyrazolyl)anthranils (13, 14, and 15)——A mixture of **1a** (0.01 mol) and MeCOCl, BzCl, or ethyl chloroformate (30 ml) was heated under stirring at 50—60° for 10 hr. MeCOCl, BzCl, or ethyl chloroformate was removed by evaporation *in vacuo* and the oily residue was triturated with saturated $NaHCO_3$ solution. The whole mixture was extracted with $CHCl_3$, and the extract was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crystalline residue was recrystallized from a suitable solvent. NMR (DMSO-d_6) δ: **13**; 2.42 and 2.72 (each 3H, each s, 2×C<u>H</u>$_3$), 2.80 (3H, s, COC<u>H</u>$_3$), 7.20—7.75 (3H, m, aromatic <u>H</u>). **14**; 2.30 and 2.70 (each 3H, each s, 2×C<u>H</u>$_3$), 7.30—8.00 (8H, m, aromatic <u>H</u>). **15**; 1.40 (3H, t, J=6 Hz, CH_2C<u>H</u>$_3$), 2.30 and 2.60 (each 3H, each s, 2×C<u>H</u>$_3$), 4.50 (2H, q, J=6 Hz, C<u>H</u>$_2CH_3$), 7.30—7.90 (3H, m, aromatic <u>H</u>).

5-Chloro-3-(3,5-dimethylpyrazolyl)anthranil (16)——A mixture of **13** (293 mg, 1 mmol) and NaOH (44 mg, 1.1 mmol) in EtOH (10 ml) was allowed to stand overnight at room temperature. EtOH was removed by concentration *in vacuo*, and the crystalline residue was recrystallized from MeOH to **16** (205 mg) (82%) as colorless needles, mp 186—187°. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH). UV λ_{max}^{EtOH} nm (log ε): 248 (4.02), 348 (3.82). NMR (DMSO-d_6) δ: 2.33 (6H, s, 2×C<u>H</u>$_3$). *Anal.* Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.27; H, 4.05, N, 16.88.

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