280, 286, 309. The IR spectrum of IV was superimposable on that of an authentic *d*-maackiain.

Genistein (V)——Colorless needles, mp 285—290°, with a purplish-brown color reaction to $FeCl_3$. UV λ_{max}^{MeOH} nm: 261, 328 (s). MS (*m/e*): 270 (M^+), 242, 153, 152, 118. Mixed mp tests and IR spectral comparison revealed this substance to be identical with authentic genistein.

V Acetate (Va): Colorless needles, mp 208—210° MS (*m/e*): 396 (M^+), 395, 354, 312, 270, 153, 152, 118.

7,3′-Dihydroxy-4′-methoxyisoflavone (VI)——Colorless needles, mp 251—253°. UV λ_{max}^{MeOH} nm: 247, 260 (s). 290, 308 (s). MS (*m/e*): 284 (M^+), 148, 137. Mixed mp tests and IR spectral comparison showed this compound to be identical with authentic 7,3′-dihydroxy-4′-methoxyisoflavone.

VI Acetate (VIa): Colorless needles, mp 205—208° MS (*m/e*): 368 (M^+), 326, 284, 148, 137

Formononetin-7-O-β-glucoside (VII)——Colorless prisms, mp 223° UV λ_{max}^{MeOH} nm: 250 (s), 259, 301 (s), PMR (TMS ether of VII, in CCl_4): 3.18—3.83 (9H, m, aliphatic H+OMe), 4.91 (1H, d, J=6.0 Hz, glucosyl anomeric H), 6.88 (2H, d, J=9.0 Hz, $C_{3',5'}$–H), 6.93 (1H, d, J=2.0 Hz, C_8–H), 6.98 (1H, dd, J=2.0 Hz, J=9.0 Hz, C_6–H), 7.46 (2H, d, J=9.0 Hz, $C_{2',6'}$–H), 7.85 (1H, s, C_2–H), 8.16 (1H, d, J=9.0 Hz, C_5–H). VII was hydrolyzed with c. HCl afforded I, and glucose was detected from the filtrate of I by PPC and TLC.

VII Acetate: Colorless needles, mp 189—191°. MS (*m/e*): 598 (M^+), 331, 271, 267, 229, 211, 169, 132, 109.

Daidzin (VIII)——Colorless needles, mp 235°. UV λ_{max}^{MeOH} nm: 256, 310 (s). VIII was hydrolyzed with c. HCl to give II and glucose. Mixed mp tests and IR spectral comparison showed this substance to be identical with authentic daidzin.

Genistin (IX)——Colorless needles, mp 249°, with a purplish-brown color reaction to $FeCl_3$. UV λ_{max}^{MeOH} nm: 228 (s), 260, 305 (s). IX was hydrolyzed with c. HCl to afford V and glucose. Mixed mp tests and IR spectral comparison revealed this compound to be identical with authentic genistin.

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Synthesis of 3-(Guaiazulen-3-yl)-3-oxopropionic Acid Derivatives[1)]

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Guaiazulene (1,4-dimethyl-7-isopropylazulene) reacted with malonyl dichloride in the absence of a Lewis acid to afford 3-(guaiazulen-3-yl)-3-oxopropionylchloride (**1**), which was converted by treatment with water into 3-(guaiazulen-3-yl)-3-oxopropionic acid (**2**) and 3-acetylguaiazulene (**3**). Upon treatment of **1** with some alcohols and aromatic amines, the corresponding esters (**4**) and amides (**5**) were obtained, respectively. The reaction of methyl 3-(guaiazulen-3-yl)-3-oxopropionate (**4a**) with hydrazine gave 3-(guaiazulen-3-yl)-3-oxopropionylhydrazide (**6**), which was easily cyclized into 5-(guaiazulen-3-yl)-2,3-dihydropyrazol-3-one (**7**).

Keywords——guaiazulene; malonyl dichloride; acylation of guaiazulene; 3-(guaiazulen-3-yl)-3-oxopropionic acid derivatives; 5-(guaiazulen-3-yl)-2,3-dihydropyrazol-3-one

It is known that the acylation of guaiazulene (1,4-dimethyl-7-isopropylazulene) with acid halides should be carried out in the presence or absence of Lewis acid, depending on the acid

1) This work was reported at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.

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halide employed.[3] Treibs[4] and Hamajima *et al.*[5] reported that oxalyl halides reacted with guaiazulene in the absence of a Lewis acid to afford (guaiazulen-3-yl)glyoxalyl halides which could be converted by treatment with alcohols and amines into (guaiazulen-3-yl)glyoxalic acid esters and amides, respectively; some of these derivatives possess anti-allergic, anti-inflammatory and anti-ulcerous activities.[6] On the other hand, it has been reported that malonyl dichloride reacted with azulene without any catalyst.[7] In the course of our study on azulene chemistry, we found that malonyl dichloride also reacted with guaiazulene in the absence of a Lewis acid to give 3-(guaiazulen-3-yl)-3-oxopropionylchloride (**1**). This paper describes the synthesis of 3-(guaiazulen-3-yl)-3-oxopropionic acid (**2**), and its ester and amide derivatives.

Reaction of guaiazulene with malonyl dichloride in anhydrous ether at −5°, followed by treatment with water gave **2** and 3-acetylguaiazulene (**3**)[3a] in 21% and 50% yields, respectively. The formation of **2** and **3** is due to the hydrolysis of **1** and the subsequent decarboxylation of **2**. In fact, the acid **2** was gradually decarboxylated into **3** at room temperature, and the reaction occurred readily on heating in benzene. Our compound **3** was identical with 3-acetylguaiazulene prepared by the acetylation of guaiazulene.[3a,8] The structure of **3** was also confirmed on the basis of NMR data; no signal due to an aromatic proton at the 3-position[8] was observed. These results indicate that the condensation of malonyl dichloride with guaiazulene occurred at the 3-position.

The chloride **1** reacted readily with methanol and ethanol at 0° to give methyl and ethyl 3-(guaiazulen-3-yl)-3-oxopropionates (**4a**) and (**4b**), respectively. The ester **4a** was identical

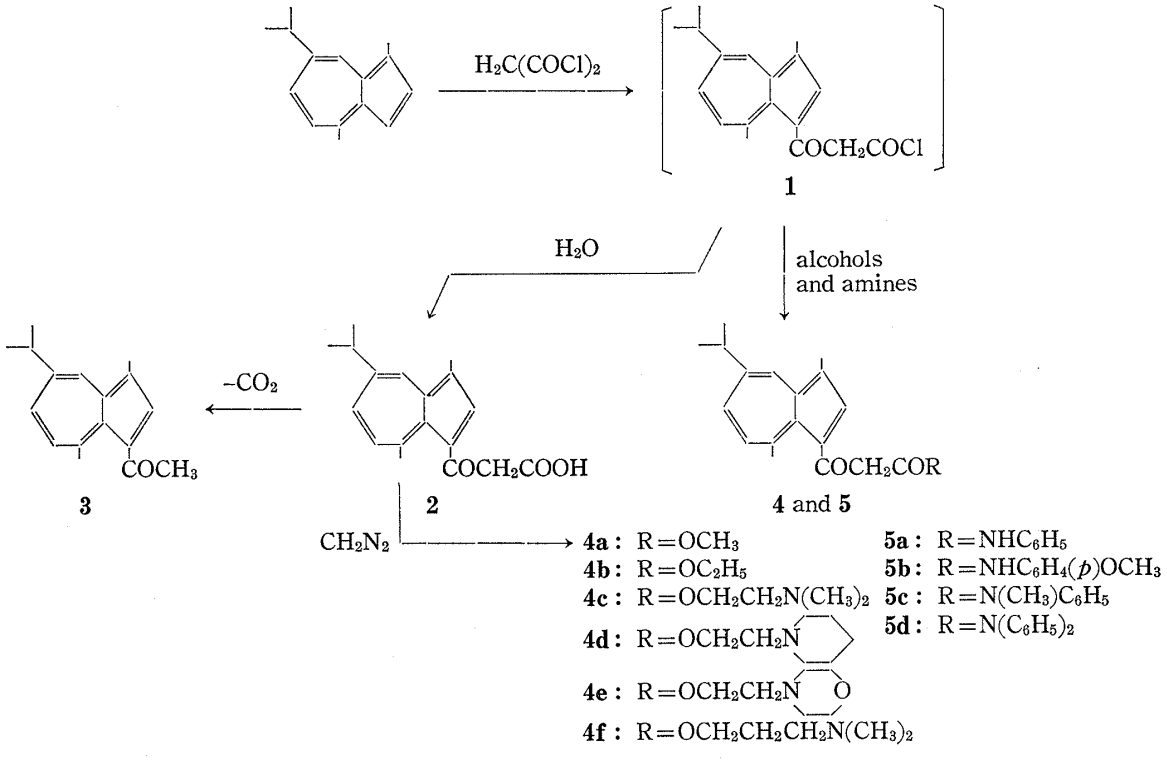

Chart 1

3) *a*) D.H. Reid, W.H. Stafford, and W.L. Stafford, *J. Chem. Soc.*, **1958**, 1118; *b*) W. Treibs, *Chem. Ber.*, **90**, 761 (1957); *c*) W. Treibs, K.H. Jost, C. Kurpjun, and G. Grundke-Schroth, *Chem. Ber.*, **94**, 1728 (1961).
4) W. Treibs, *Chem. Ber.*, **92**, 2152 (1957).
5) R. Hamajima, K. Iwano, and H. Okuda, *Yakugaku Zasshi*, **98**, 1101 (1978).
6) R. Hamajima and H. Okuda, Jpn Kokai Tokkyo Koho, 7877043 (1978); 7877044 (1978); 77153979 (1977).
7) W. Treibs and B. Streckenbach, *Chem. Ber.*, **94**, 1734 (1961).
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with that obtained by the reaction of **2** with diazomethane. Analogously, **1** was reacted with several diakylaminoalcohols to give the corresponding esters (**4c—f**) (Chart 1), which were isolated as the hydrochlorides (Table I).

In order to obtain 3-(guaiazulen-3-yl)-3-oxopropionic acid amide derivatives, we also attempted to react **1** with amines. When an ethereal solution of **1** was treated with methylamine, ethylamine and hydrazine in tetrahydrofuran, multiple unknown products were formed; the expected amide could not be isolated. In contrast, **1** reacted with aromatic amines, such as aniline, *p*-anisidine, methylaniline and diphenylamine, to give the corresponding N-substituted 3-(guaiazulen-3-yl)-3-oxopropionamides (**5a—d**) (Chart 1, Table II).

Table I. 3-(Guaiazulen-3-yl)-3-oxopropionates **4**

Comp No.	mp (°C)	Yield (%)	Formula[a]	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} (cm^{-1}) (CO ester)	(CO ketone)
4c	194—195	62	$C_{22}H_{30}ClNO_3$	67.42 (67.59	7.72 7.64	3.57 3.55)	1730	1645
4d	176—179	28	$C_{25}H_{34}ClNO_3$	69.51 (69.24	7.93 7.90	3.24 3.19)	1735	1650
4e	166—168	18	$C_{24}H_{32}ClNO_4$	66.42 (66.12	7.43 7.43	3.23 3.21)	1730	1660
4f	156—157	32	$C_{23}H_{32}ClNO_3$	68.05 (67.70	7.95 7.84	3.45 3.44)	1730	1660

a) Isolated as the hydrochlorides.

Table II. 3-(Guaiazulen-3-yl)-3-oxopropionamides **5**

Comp. No.	mp (°C)	Yield (%)	Formula	MS *m/e* (M$^+$)	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} (cm^{-1}) (NH)	(CO)
5a	108—109	63	$C_{24}H_{25}NO_2$	359	80.19 (80.12	7.01 7.01	3.90 3.92)	3330	1670 1645
5b	159—159.5	59	$C_{25}H_{27}NO_3$	389	77.09 (77.16	6.99 6.89	3.60 3.38)	3320	1680 1640
5c	Oil	56	$C_{25}H_{27}NO_2$	373	80.39 (80.24	7.29 7.34	3.75 3.47)		1660 1630[a]
5d	157—158	63	$C_{30}H_{29}NO_2$	435	82.73 (82.48	6.71 6.72	3.22 3.21)		1675 1610

a) Measured by means of a sodium chloride plate.

Treibs *et al.*[7] reported that methyl 3-(azulen-1-yl)-3-oxopropionate reacted with hydrazine, phenylhydrazine and hydroxylamine in boiling ethanol to afford the pyrazolone, phenylpyrazolone and isoxazolone derivatives, respectively, in moderate yields. We examined the condensation of the ester **4a** with several carbonyl reagents. Upon heating with an excess of hydrazine hydrate in methanol for 30 min, **4a** afforded only 3-(guaiazulen-3-yl)-3-oxopropionylhydrazide (**6**) in 89% yield. When the same reaction was carried out by heating for 15 hr, 5-(guaiazulen-3-yl)-2,3-dihydropyrazol-3-one (**7**, 15% yield) was obtained, together with a compound $C_{21}H_{26}N_2O_2$ (**8**), whose structure was not elucidated (Chart 2). The cyclization of **6** to **7** was accomplished quantitatively in methanol containing hydrochloric acid. Phenylhydrazine and hydroxylamine, however, did not react with **4a** under the same conditions.

The condensation of the carbonyl reagents with methyl 3-(azulen-1-yl)-3-oxopropionate[7] proceeded through initial addition of the carbonyl reagents to the keto-carbonyl group of the β-ketoester. Therefore, the behavior of **4a** towards hydrazine, phenylhydrazine and hydroxyl-

amine may be interpreted in terms of the steric effect of the 4-methyl group at the peri-position with respect to the keto-carbonyl group of **4a**.

The structures of all the new compounds obtained were deduced from their analytical and spectral data.

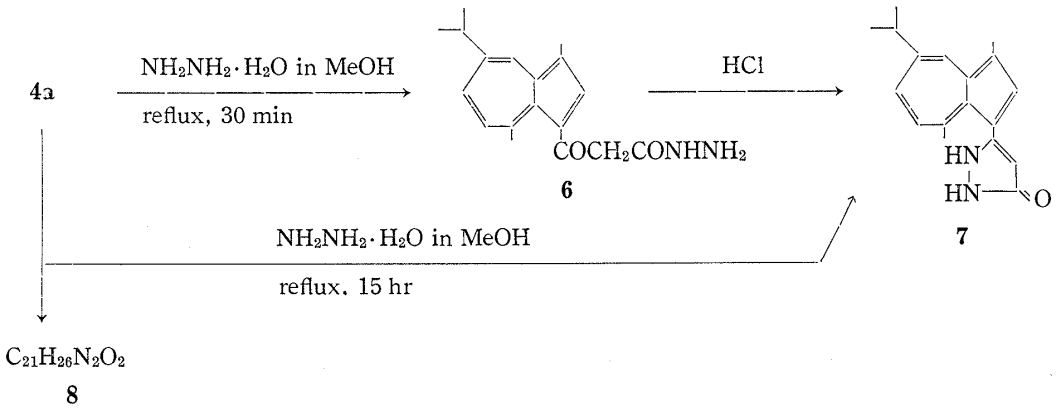

Chart 2

Experimental

All melting points were determined in a capillary tube and uncorrected. Infrared (IR) spectra were recorded on a Hitachi 251 spectrometer, nuclear magnetic resonance (NMR) spectra on a JEOL JNM-C-60H spectrometer with tetramethyl silane as an internal standard. Mass spectra were obtained on a JEOL JNM-01SG spectrometer by the direct insertion technique.

3-(Guaiazulen-3-yl)-3-oxopropionic Acid (2) and 3-Acetylguaiazulene (3)——A solution of malonyl dichloride (1.7 g, 12 mmol) in anhyd. ether (10 ml) was added dropwise to a solution of guaiazulene (2 g, 10 mmol) in anhyd. ether (50 ml) at −5° with stirring. The whole was stirred for 20 min under ice-cooling, then water (50 ml) was added dropwise to the reaction mixture. The organic layer was separated, extracted with 5% NaOH and washed with water. The extract was dried over $MgSO_4$, then the solvent was evaporated off to give a residue, which was recrystallized from petroleum-ether–$CHCl_3$ to afford 1.2 g (50%) of **3** as deep violet plates, mp 87—88° (lit.[3a] mp 88.2—88.8°). The IR spectrum was identical with that of **3** obtained by the method of Reid *et al.*[3a] NMR ($CDCl_3$) ppm: 1.37 (6H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.62 (3H, s, 1-CH_3), 2.73 (3H, s, $COCH_3$), 2.93 (3H, s, 4-CH_3), 3.14 (1H, m, $C\underline{H}(CH_3)_2$), 7.32 (1H, d, J=11 Hz, 5-H), 7.63 (1H, dd, $J_{5,6}$=11 Hz, $J_{6,8}$=2 Hz, 6-H), 7.97 (1H, s, 2-H), 8.23 (1H, d, J=2 Hz, 8-H).

The NaOH extract was acidified with 10% HCl and extracted with ether. The ethereal extract was dried over $MgSO_4$, and then cooled at 0° to precipitate **2** as a brown crystalline solid (0.6 g, 21%), mp 88—89° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1740 (CO), 1580.

Decarboxylation of 2 into 3——A solution of **2** (10 mg) in benzene (5 ml) was refluxed for 20 min. After removal of the solvent, the residue was recrystallized from petroleum-ether–$CHCl_3$ to yield 7.6 mg (90%) of **3**, mp 88—89° (lit.[3a] mp 88.2—88.8°).

Methyl and Ethyl 3-(Guaiazulen-3-yl)-3-oxopropionates (4a and 4b)——a) **2** (0.28 g) was dissolved in an ethereal solution of diazomethane. The solution was allowed to stand for 1 hr at room temperature, then the solvent was removed to yield a residue which was chromatographed on an alumina column (10 g) with $CHCl_3$ (100 ml). The eluate was concentrated and the residue was dried *in vacuo* to yield 0.24 g (80%) of **4a** as a viscous oil. Thin-layer chromatography (TLC) (Rf=0.43, Merck Kieselgel 60 F_{254}, $CHCl_3$). IR ν_{max} cm^{-1}: 2950 (CH), 1730 (CO ester), 1640 (CO ketone). NMR ($CDCl_3$) ppm: 1.36 (6H, d, J=6 Hz, CH-$(C\underline{H}_3)_2$), 2.58 (3H, s, 1-CH_3), 2.93 (3H, s, 4-CH_3), 3.12 (1H, m, $C\underline{H}(CH_3)_2$), 3.73 (3H, s, $COOCH_3$), 4.08 (2H, s, $COCH_2CO$), 7.32 (1H, d, J=11 Hz, 5-H), 7.58 (1H, dd, $J_{5,6}$=11 Hz, $J_{6,8}$=2 Hz, 6-H), 7.89 (1H, s, 2-H), 8.23 (1H, d, J=2 Hz, 8-H). *Anal.* Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.16; H, 7.16.

b) A solution of malonyl dichloride (1.7 g, 12 mmol) in anhyd. ether (20 ml) was added dropwise, with stirring, to a solution of guaiazulene (2 g, 10 mmol) in anhyd. ether (100 ml) at 0° to yield an ethereal solution of the chloride **1**. Methanol (1 ml) was added to this solution under ice-cooling. After being stirred for 20 min at room temperature, the mixture was poured into ice-water and the organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on an alumina column (20 g) with $CHCl_3$ (150 ml) to yield 1.9 g (63%) of **4a**.

Ester **4b** was obtained as an oil by the same method, upon treating the ethereal solution of **1** with ethanol in place of methanol; yield 1.9 g (61%). TLC (Rf=0.43, Merck kieselgel 60 F_{254}, $CHCl_3$). IR ν_{max} cm^{-1}: 2940 (CH), 1725 (CO ester), 1635 (CO ketone). NMR ($CDCl_3$) ppm: 1.21 (3H, t, J=4 Hz, $COOCH_2C\underline{H}_3$), 1.37

(6H, d, J=7 Hz, CH(C<u>H</u>$_3$)$_2$), 2.59 (3H, s, 1-CH$_3$), 2.93 (3H, s, 4-CH$_3$), 3.13 (1H, m, C<u>H</u>(CH$_3$)$_2$), 4.04 (2H, s, COCH$_2$CO), 4.18 (2H, q, J=4 Hz, COOC<u>H</u>$_2$CH$_3$), 7.30 (1H, d, J=11 Hz, 5-H), 7.57 (1H, dd, $J_{5,6}$=11 Hz, $J_{6,8}$=2 Hz, 6-H), 7.88 (1H, s, 2-H), 8.21 (1H, d, J=2 Hz, 8-H). *Anal.* Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.50; H, 7.72.

Synthesis of Esters (4c—f)——An ethereal solution of **1**, prepared by the method described above, was added dropwise to a mixture of anhyd. Na_2CO_3 (2.5 g) and 30 mmol of dialkylaminoalcohol in anhyd. dimethylformamide (DMF) (45 ml) with stirring at −5°. After being stirred at room temperature for 1.5 hr, the mixture was poured into ice-water. The resulting solution was extracted with ether. The ethereal layer was again extracted with 10% HCl. The acid layer was extracted with $CHCl_3$, and the extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was recrystallized from $CHCl_3$–*n*-hexane to afford the hydrochlorides of **4c—f** (Table I) as deep green prisms.

Synthesis of Amides (5a—d)——An ethereal solution of **1** was added dropwise, with stirring, to a mixture of anhyd. Na_2CO_3 (2.5 g) and aniline (1.9 g 20 mmol) in anhyd. DMF (30 ml) under ice-cooling. After being stirred at room temperature for 3 hr, the mixture was poured into ice-water. The resulting solution was extracted with benzene and the benzene layer was washed with 5% HCl and water, dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was chromatographed on a silica gel column (50 g) with iso-propylether (300 ml). The eluate was concentrated *in vacuo* and the residue was recrystallized from benzene–*n*-hexane to yield **5a** as dark blue prisms (Table II). NMR ($CDCl_3$) ppm: 1.38 (6H, d, J=7 Hz, CH(C<u>H</u>$_3$)$_2$), 2.85 (3H, s, 1-CH$_3$), 2.92 (3H, s, 4-CH$_3$), 3.11 (1H, m, C<u>H</u>(CH$_3$)$_2$), 4.15 (2H, s, COCH$_2$CO), 7.03—8.03 (10H, m, NH and aromatic).

5b—d were obtained by the method described for synthesis of **5a**, with *p*-anisidine, N-methylaniline and diphenylamine, respectively, in place of aniline.

5b was purified by column chromatography [silica gel (50 g), $CHCl_3$–iso-propylether (5: 1, 300 ml)] and by subsequent recrystallization from $CHCl_3$–*n*-hexane. Dark violet needles (Table II).

5c was purified by column chromatography [silica gel (50 g), $CHCl_3$–iso-propylether (5: 1, 300 ml)]. Dark blue viscous oil (Table II).

5d was purified by column chromatography [silica gel (50 g), ether–$CHCl_3$ (1: 5, 300 ml)] and by subsequent recrystallization from ether–$CHCl_3$. Dark blue prisms (Table II).

3-(Guaiazulen-3-yl)-3-oxopropionylhydrazide (6)——A solution of **4a** (1.0 g) and hydrazine hydrate (1.0 g) in methanol (30 ml) was refluxed for 30 min. After removal of the solvent, the residue was triturated with *n*-pentane (20 ml) and the resulting solid was recrystallized from benzene–*n*-hexane to give 0.9 g (90%) of **6** as deep blue prisms, mp 102.5—103.5°. IR ν_{max}^{KBr} cm^{-1}: 3255 (NH), 1660 (CO ketone), 1630 (CO amide). NMR ($CDCl_3$) ppm: 1.35 (6H, d, J=7 Hz, CH(C<u>H</u>$_3$)$_2$), 2.55 (3H, s, 1-CH$_3$), 2.85 (3H, s, 4-CH$_3$), 3.12 (1H, m, C<u>H</u>(CH$_3$)$_2$), 3.91 (2H, s, NH$_2$), 4.00 (2H, s, COCH$_2$CO), 7.31—8.20 (4H, m, aromatic), 8.28 (1H, s, NH). MS *m/e*: 298 (M$^+$). *Anal.* Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.29; H, 7.41; N, 9.36.

5-(Guaiazulen-3-yl)-2,3-dihydropyrazol-3-one (7) and Compound (8)——A solution of **4a** (0.5 g) and hydrazine hydrate (0.5 g) in methanol (15 ml) was refluxed for 15 hr, then cooled. Ether was added to the reaction mixture and the resulting crystalline solid (crude **7**) was collected by filtration. Recrystallization from dioxane gave 70 mg (15%) of **7** as blue prisms, mp>300°. IR ν_{max}^{KBr} cm^{-1}: 1615 (CO). MS *m/e*: 280 (M$^+$). *Anal.* Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.00; H, 7.21; N, 9.99.

The filtrate was concentrated *in vacuo*. The residue was dissolved in benzene and the benzene solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from benzene–*n*-hexane to yield 0.38 g of **8** as blue prisms, mp 129—129.5°. IR ν_{max}^{KBr} cm^{-1}: 1670, 1645 (CO). MS *m/e*: 338 (M$^+$). *Anal.* Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: 74.50; H, 7.75; N, 8.27.

Cyclization of 6 into Pyrazolone (7)——A solution of **6** (0.3 g) in 10% methanolic HCl (20 ml) was refluxed for 10 min, then cooled. The resulting precipitates was collected by filtration and recrystallized from dioxane to yield 0.27 g (96%) of **7** as blue prisms.