dinone **15b**. A solution of 400 mg (1.7 mmol) of **19** in 15 ml of ethanol containing 2 ml of 6 *N* hydrochloric acid was refluxed for 4 hr. Then the solution was made alkaline (aqueous sodium hydroxide), extracted ($CHCl_3$), dried (Na_2SO_4), and concentrated to give 132 mg (36%) of the triazolinone **18** and 30 mg (14%) of 1,2-diethylsemicarbazide which was formed by hydrolysis of **19**.

Acknowledgments. We thank Messrs. Toshihiro Tani and Kosaku Sugimoto for their assistance in the experiment and Mr. Yasuo Choki of Takeda Chemical Ind., Ltd., for his help in nmr measurements.

Registry No.—**1a,** 39169-68-1; **1b,** 39169-67-0; **1c,** 52225-94-2; **1d,** 52225-95-3; **1e,** 6794-94-1; **2,** 525-06-4; **3a,** 39169-70-5; **3b,** 39169-69-2; **3c,** 52225-96-4; **3d,** 52225-97-5; **4,** 52225-98-6; **7,** 6336-52-3; **9,** 52225-99-7; **10a,** 103-71-9; **10b,** 4461-33-0; **11,** 52225-74-8; **12,** 52225-75-9; **14,** 5040-62-0; **15a,** 52225-76-0; **15b,** 52225-77-1; **17,** 52225-78-2; **18,** 52225-79-3; **19,** 52225-80-6; **22a,** 44650-07-9; **22b,** 52225-81-7; **22e,** 2303-97-1; **22f,** 52225-82-8; **23,** 52225-83-9; **24,** 52225-84-0.

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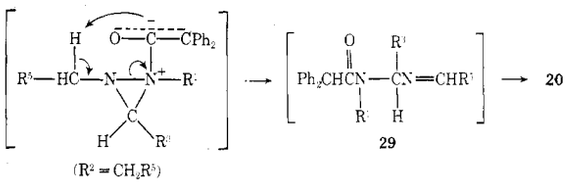
(30) The following mechanism leading to the intermediate **20** is also possible. This participation of an *N*-alkyl substituent in the reaction would be



compatible with the fact that the similarly acidic hydrogen on the ring carbon of an oxaziridine was not abstracted in the reaction with diphenylketene. The reactions with isocyanates can also be elucidated by the above mechanism including the abstraction of an α hydrogen on a N substituent. Thus further study of the mechanism is of future interest.

Studies on Ketene and Its Derivatives. LXIII.[1] Reaction of Diketene with Azobenzenes

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Irradiation of the solution of symmetric azobenzenes (**1a–k**) and diketene in chloroform resulted in the formation of 1:1 cycloadduct, 1,2-diarylhexahydropyridazine-3,5-dione (**2a–k**). Using asymmetric azobenzenes such as **1l–u**, the cycloaddition reaction occured stereoselectively to result in the formation of 1-(4-alkoxyphenyl)-2-arylhexahydropyridazine-3,5-dione (**2l–u**). The possible reaction mechanism is also discussed.

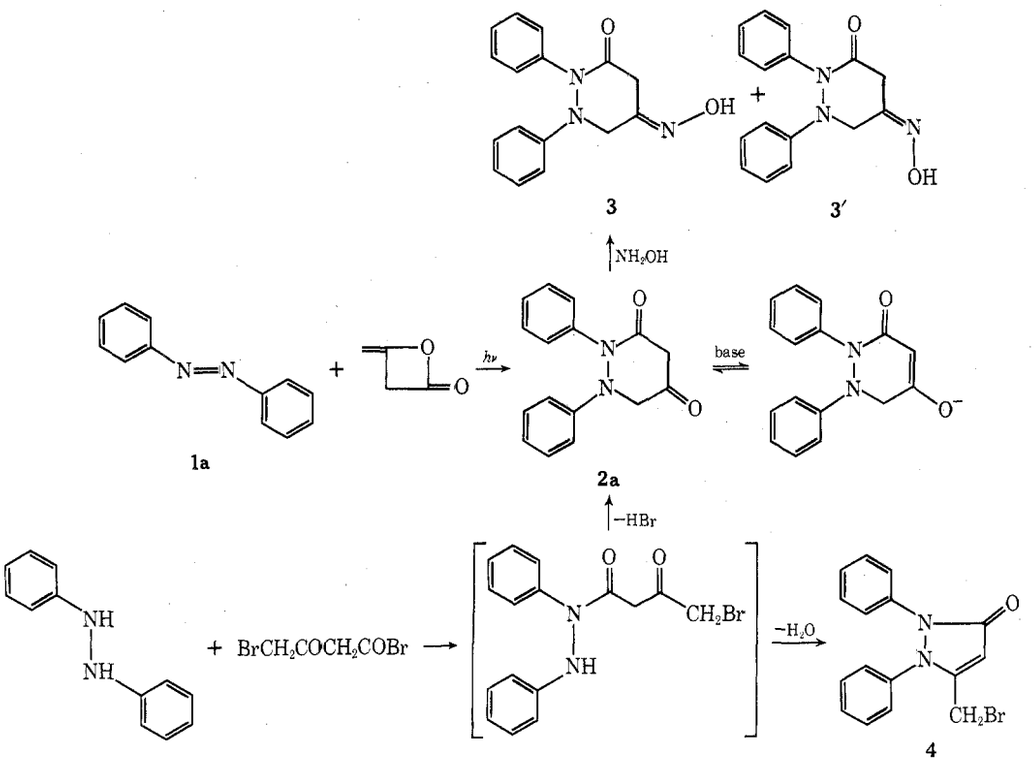
The cycloaddition of azo compounds with ketene is well known,[2] but reactions of azo compounds with diketene have not been reported. The present paper describes a study of reactions of diketene and azobenzenes to give 1,2-diarylpyridazinedione derivatives (**2**).

Refluxing of a solution of diketene and azobenzene (**1a**) in dry chloroform resulted in the recovery of starting materials; however, irradiation of the solution with stirring at room temperature gave rise to the 1:1 adduct (**2a**) in 62% yield. The ir spectrum of **2a** showed two carbonyl bands at 1746 and 1688 cm^{-1} ascribable to ketone and amide group, respectively. The nmr spectrum ($CDCl_3$) showed two singlet signals at 3.35 (2 H, $COCH_2CO$) and 4.34 ppm (2 H, NCH_2CO).

Compound **2a** was insoluble in acid, and negative for the ferric chloride test. However, **2a** was enolized readily with base. In base the 1745-cm^{-1} ir band disappeared and the amide carbonyl band shifted from 1688 to 1635 cm^{-1}. Reaction of **2a** with hydroxylamine afforded an oxime which from nmr data was a 1:1 mixture of stereoisomers (**3** and **3′**).

These data are consistent with the structure of **2a** as 1,2-diphenylhexahydropyridazine-3,5-dione, and a reference sample was obtained in 1.5% yield by condensation of hydrazobenzene with ω-bromoacetoacetyl bromide. The main product was 5-bromomethyl-1,2-diphenyl-3-pyrazolone (**4**) (Scheme I).

Scheme I



Ten symmetrical disubstituted azobenzenes (**1b–k**) were subjected to the same reaction. The corresponding 1,2-diarylhexahydropyridazine-3,5-dione derivatives (**2b–k**) were obtained in moderate yields with the exception of the dichloro- and 2,2′-dimethoxyazobenzenes (**1e,g,h**). Only the starting azo compounds were recovered in these cases. The results in hexane, dichloromethane, or excess diketene did not differ appreciably.

Although yields are not so high, the method is a convenient source for the preparation of the previously unknown 1,2-diarylhexahydropyridazinedione derivatives. The results are summarized in Table I.

The cycloaddition was carried out also with asymmetrical disubstituted azobenzenes such as 4-methoxy-4′-substituted azobenzenes (**1l–u**) (Table II). A single product corresponding to the 1:1 adduct (**2**) was isolated in each case in yields comparable to those with the symmetrical azobenzenes. Though two isomers are possible, the nmr spectra of the products (**2l–u**) indicate that the 4-methoxyphenyl group is attached to N-1 (NCH_2CO) rather than N-2 (NCO). A singlet or closely spaced multiplet for four aromatic protons is observed around 6.8 ppm, while another signal due to aromatic protons appears around 7.2–7.8 ppm as a multiplet. Comparison of the signal patterns of aromatic ring protons of **2l–u** with those of **2a–k** revealed that the characteristic sharp signals around 6.8 ppm seemed to be due to the 4-alkoxyphenyl group; namely, in the nmr spectra of **2a–k**, only **2j** and **2k** showed a four-proton singlet signal at 6.80 ppm (see Table I). Accordingly, signals around 6.8 ppm of **2l–u** should be due to 4-alkoxyphenyl ring protons.

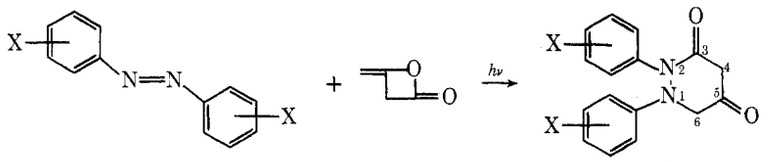
Moreover, it is known that signals of aminophenyl ring protons appear at higher field region than those of acylaminophenyl ring protons.[3] For instance, *p*-anisidine shows its ring protons at 6.68 and 6.73 ppm as an overlapped doublet signal. In contrast *p*-acetoanisidine shows a typical AB quartet signal at 6.77 ppm (2 H, J = 9 Hz) related to the ring protons at the ortho position to the methoxy group, and at 7.36 ppm (2 H, J = 9 Hz) to those at the ortho position to the acetamide group.

From the data described above, it is reasonably concluded that the 4-methoxyphenyl group is fixed to the 1 position of the pyridazine ring (NCH_2CO), and its ring protons appear as a characteristic singlet or overlapped doublet signal around 6.8 ppm.

Although **2** was not reduced by catalytic reduction, treatment of **2l** with sodium borohydride gave rise to the alcohol (**5l**) as an oil, which was dehydrated to give the tetrahydropyridazin-3-one (**6l**). Reaction of **2l** with acetyl chloride or tosyl chloride gave the enol esters, **7** or **8**, respectively (Scheme II). Heating of **2** and **5** with dilute acid or alkali gave a resinous product. Attempts to cleave the N–N bond of these pyridazine derivatives by catalytic hydrogenolysis were not successful.

The use of an nmr shift reagent with the tetrahydropyridazinone (**6o**) provided a further indication that the 4-alkoxyphenyl moiety is present at N-1. Namely, the nmr spectra of **6o** were measured after successive addition of $Eu(fod)_3$ and the field positions of the nmr lines (δ_E) were plotted as a function of metal concentration (Figure 1). Since an amide group is a weak Lewis base, the observed S values, the europium shift parameters, were rather small, but it was revealed that each proton resonance was affected

Table I
Reaction of Diketene with Symmetric Azobenzenes

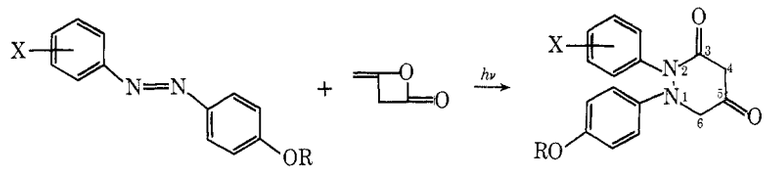


1a–k 2a–k

2[a]	X	Reaction conditions: Solvent[b]	Time, hr	Yield,[c] %	Mp, °C	Ir, ν_{max} (CHCl$_3$), cm^{-1}: Keto	Amide	Nmr, δ (CDCl$_3$), ppm: 4-CH$_2$	6-CH$_2$	Aromatic
a	H	C	48	62	148	1746	1688	3.35	4.34	6.8–7.9 (m, 10 H)
b	2-CH$_3$	C	48	60	167 dec	1739	1643	3.69	4.16	7.0–7.34 (m, 8 H)
c	3-CH$_3$	B	72	46	170.5 dec	1748	1687	3.36	4.34	6.78–7.65 (m, 8 H)
d	4-CH$_3$	C	35	53	104.5	1745	1682	3.14	4.17	6.67 and 7.04 (AB q, 2 H, 2 H, J = 9 Hz), 7.08 and 7.65 (AB q, 2 H, 2 H, J = 9 Hz)
e	2-Cl	C	72							
f	3-Cl	C	48	3	152.5	1750	1696	3.38	4.35	6.82–7.85 (m, 8 H)
g	4-Cl	C	72							
h	2-OCH$_3$	C	36							
i	3-OCH$_3$	C	36	27	145.5	1745	1686	3.38	4.33	6.40–7.50 (m, 8 H)
j	4-OCH$_3$	C	24	63	144.5	1747	1681	3.35	4.28	6.80 (s, 4 H), 6.85 and 7.66 (AB q, 2 H, 2 H, J = 8 Hz)
k	4-OEt	C	43	52	119	1743	1678	3.34	4.27	6.80 (s, 4 H), 6.80 and 7.66 (AB q, 2 H, 2 H, J = 9 Hz)

[a] Satisfactory analytical values (±0.30% for C, H, and N) were reported for **2a–k.** [b] Solvents: C = chloroform, B = benzene. [c] Yields indicated do not reflect recovery of unreacted starting material.

Table II
Reaction of Diketene with Asymmetric Azobenzenes



1l–u 2l–u

2[a]	X	R	Reaction conditions: Solvent[b]	Time, hr	Yield,[c] %	Mp, °C	Ir, ν_{max} (CHCl$_3$), cm^{-1}: Keto	Amide	Nmr, δ(CDCl$_3$), ppm: 4-CH$_2$	6-CH$_2$	1-Ar[d]	2-Ar
l	H	CH$_3$	B	72	62	143	1742	1683	3.38	4.31	6.83	7.25–7.82 (m, 5 H)
m	2-CH$_3$	CH$_3$	B	48	36	135.5	1745	1676	3.50	4.33	6.90 6.91	~7.25 (m, 4 H)
n	3-CH$_3$	CH$_3$	C	24	32	81	1745	1686	3.35	4.28	6.81	~7.32 (m, 4 H)
o	4-CH$_3$	CH$_3$	C	24	44	143	1746	1682	3.34	4.28	6.81	7.15 and 7.67 (AB q, 2 H, 2 H, J = 8 Hz)
p	2-Cl	CH$_3$	C	48								
q	3-Cl	CH$_3$	C	40	28	110	1746	1688	3.36	4.28	6.82	7.10–7.86 (m, 4 H)
r	4-Cl	CH$_3$	C	48	55	138	1748	1685	3.37	4.30	6.82	7.32 and 7.81 (AB q, 2 H, 2 H, J = 7 Hz)
s	4-Br	CH$_3$	C	36	21	142	1747	1685	3.39	4.31	6.83	7.48 and 7.79 (AB q, 2 H, 2 H, J = 7 Hz)
t	4-NO$_2$	CH$_3$	C	48								
u	H	C$_2$H$_5$	B	24	50	109.5	1744	1688	3.38	4.30	6.81	7.20–7.87 (m, 5 H)

[a] Satisfactory analytical values (±0.30% for C, H, and N) were reported for **2l–u.** [b] Solvents: B = benzene, C = chloroform. [c] Yields indicated do not reflect recovery of unreacted starting material. [d] Characteristic singlet or overlapped doublet signal (4 H).

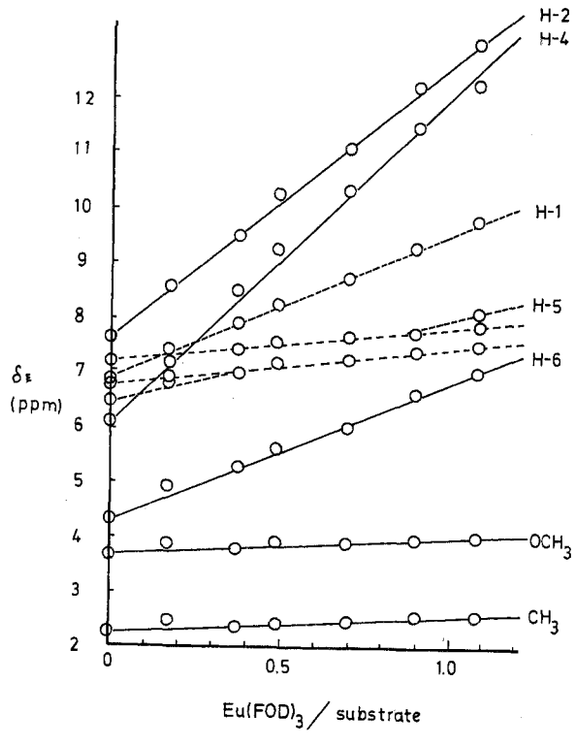
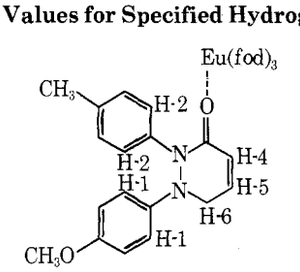


Figure 1. The relationship between chemical shifts and the molar ratio of Eu(fod)$_3$/substrate (**6o**).

by the contact shift to a different degree, and as shown in Table III, the relation between parameter S and distance r

Table III
S^a and r^b Values for Specified Hydrogens of 6o



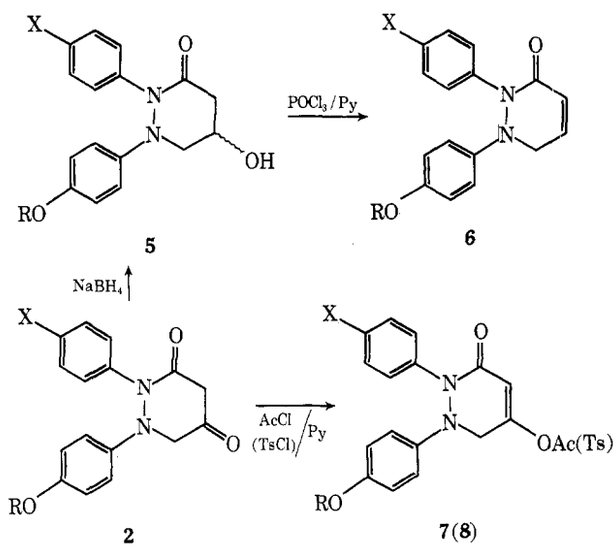
H_i	S	r, Å	K^c
1	2.7	4.41	231.57
2	4.6	3.87	266.61
4	6.2	3.35	233.06
5	1.5	5.30	223.31
6	2.1	5.46	341.82

[a] Europium shift parameter, defined in the equation $\delta_E = \delta + S$ Eu(fod)$_3$/substrate. δ_E and δ (chemical shift in the uncomplexed substrate) are in parts per million relative to TMS. [b] Average distance between the hydrogen (H_i) and the metal ion (radius Eu^{3+} = 0.95 Å) complexed with amide carbonyl group. [c] Paramagnetic shift ($\Delta\delta = \delta_E - \delta$) is dominated by the pseudo-contact interaction; $\Delta\delta_i = K/r_i^3$, where K is assumed constant for a particular solution composition and temperature.[8]

from the center of the europium ion was fairly good except for H-6.

The signals centered at 6.10 (H-4) and 7.63 ppm (aromatic, H-2) showed the greatest shift, suggesting the closest protons to the metal ion in the complex. Other aromatic protons centered at 6.81–6.84 ppm (H-1) were affected

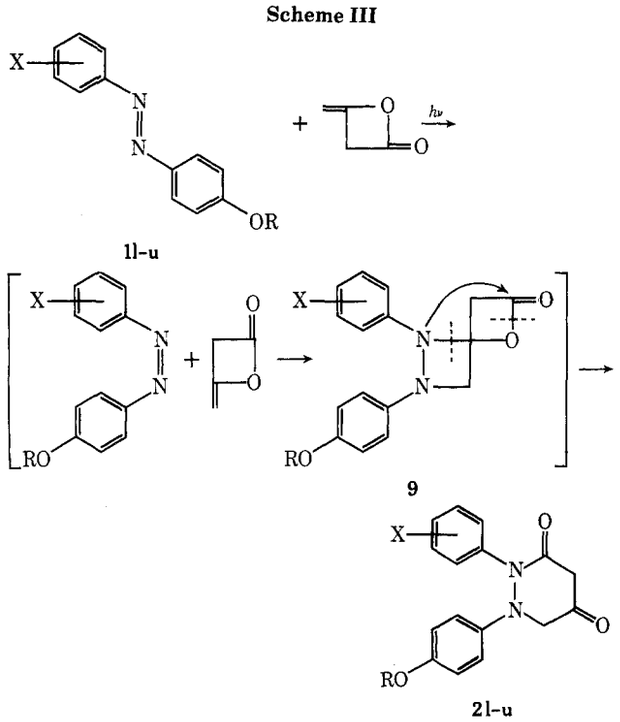
Scheme II



moderately with the contact shift. This fact is consistent with the structure of **6o** as 1-(4-methoxyphenyl)-2-(*p*-tolyl)tetrahydropyridazin-3-one, but not as the 1-(*p*-tolyl)-2-(4-methoxyphenyl) isomer.

Though details of the mechanism of the formation of the cycloadduct are not clear at present, a likely pathway is shown in Scheme III. It is already known that *trans*-azo-

Scheme III



benzene reacts with ketene only very slowly while the cis isomer reacts readily even at low temperature, and that *trans*-azobenzene is converted to the cis isomer by irradiation with uv light.[4] On the other hand, homolytic addition of the olefinic group of diketene gives a spiro compound; for instance, addition of a carbene generated from a diazo compound such as diazoacetophenone to the C=C double bond of diketene gave the spiro compound, 2-benzoyl-1-hydroxycyclopropaneacetic acid β-lactone.[5]

In this view, 1,2-cycloaddition of *cis*-azobenzene with the C=C double bond of diketene gives rise to a four-mem-

bered spiro adduct as an intermediate (**9**), which, on rearrangement, is converted to **2**.

Experimental Section

Melting points were determined by a calibrated Yanagimoto melting point apparatus. Ir spectra were measured by a Jasco DS-301 spectrometer. Nmr spectra were measured on Hitachi Perkin-Elmer R-20 and Varian A-60 spectrometers in $CDCl_3$ solution, and reported as δ values (parts per million) relative to TMS. Uv spectra were measured by a Beckman DB-G spectrometer. Mass spectra were obtained on a Hitachi RMU-7L double-focusing mass spectrometer.

Materials. Symmetric azobenzenes used in the present experiment were prepared from the corresponding nitrobenzenes by alkaline reduction with zinc dust in methanol[6] or the Drynap reduction in methanol.[7] Asymmetric azobenzenes were also prepared from appropriately substituted anilines and phenol by diazo coupling followed by alkylation with dialkyl sulfate.

General Procedure for Preparation of 1,2-Diarylhexahydropyridazine-3,5-diones (2). A solution of **1** (0.025–0.05 mol) and diketene (0.5 mol) in dry $CHCl_3$ or benzene (80–120 ml) was irradiated with uv light while being stirred for 24–72 hr at room temperature. The light source was a Riko UVL-400HA water-cooled high-pressure mercury lamp (Pyrex filter) and the reaction vessel was equipped with a drying tube. After evaporation of excess diketene under reduced pressure, the reddish-brown tar was dissolved in benzene, and the benzene solution was then extracted with 5% NaOH. The alkaline solution was acidified with 10% HCl and extracted again with benzene. The benzene solution was washed with water and dried over Na_2SO_4. Evaporation of benzene gave a brown solid which was chromatographed over silica gel to give **2** as colorless to pale orange needles. Each product was recrystallized from benzene-hexane mixture or ethanol. The results are summarized in Tables I and II.

With use of a low-pressure mercury lamp, yields were rather low and the photopolymerization of diketene occurred prior to the cycloaddition reaction.

Reaction of Hydrazobenzene with ω-Bromoacetoacetyl Bromide. A solution of ω-bromoacetoacetyl bromide (13.5 g) in CCl_4 (100 ml) was added dropwise at 0° to a solution of hydrazobenzene (9.2 g) in $CHCl_3$ (200 ml). After stirring vigorously for 30 min, the reaction mixture was filtered and the residue was washed with $CHCl_3$. The filtrate and the $CHCl_3$ washing were combined and extracted with 5% NaOH. The alkaline solution was acidified with 10% HCl and then extracted with benzene. The benzene solution was washed with water and dried over Na_2SO_4.

Evaporation of the benzene gave **2a** as colorless needles (200 mg, 1.5%), mp 147°.

After extraction with 5% NaOH, the $CHCl_3$ layer was condensed to give a crystalline residue, which was purified by recrystallization to give colorless needles of **4**: mp 135°; yield 7.1 g (43%); ir ($CHCl_3$) 2980, 1660, 1595, 1490, 1380 cm^{-1}; nmr δ 4.15 (s, 2 H, $-CH_2Br$), 5.97 (s, 1 H, 4-CH=), ~7.46 ppm (m, 10 H, aromatic protons); mass spectrum *m/e* 330, 328 (M^+, base peak), 249, 183, 181, 144, 130, 104, 77.

Anal. Calcd for $C_{16}H_{13}BrN_2O$: C, 58.37; H, 3.98; N, 8.51. Found: C, 58.53; H, 3.88; N, 8.65.

1,2-Diphenyltetrahydropyridazine-3,5-dione 5-Oxime (3a and 3a'). An EtOH solution of **2a** (500 mg in 30 ml) was treated with an aqueous solution of $NH_2OH \cdot HCl$ and Na_2CO_3 (140 and 210 mg in 20 ml). After the mixture was stirred for 1.5 hr at 60°, the solvent was evaporated under reduced pressure to afford a yellow oil which was then extracted with ether. The ether layer was washed with 5% NaOH and water and dried over Na_2SO_4. Evaporation of the ether gave the oxime, a mixture of **3a** and **3a'**, as colorless crystals (430 mg, 81%): mp 168–174°; ir ($CHCl_3$) 3550, 3000, 1670, 1645, 1510, 1360, 1200 cm^{-1}; nmr ($CDCl_3$) δ 3.24 (s, 1.1 H, 4-CH_2 of **3a'**), 3.45 (s, 0.9 H, 4-CH_2 of **3a**), 4.52 (s, 0.9 H, 6-CH_2 of **3a**), 4.73 (s, 1.1 H, 6-CH_2 of **3a'**), 6.80–7.90 (m, 10 H, aromatic protons), 8.28–8.55 ppm (broad, 1 H, –OH, the signal disappeared upon addition of a small amount of D_2O); mass spectrum *m/e* 281 (M^+, base peak), 253, 236, 195, 183, 176, 131, 130, 119, 106, 105, 104, 93, 91, 78, 77.

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.29; H, 5.38; N, 14.50.

Attempts to isolate syn and anti isomers were not successful.

1-(4-Methoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (6l). To an EtOH solution of **2l** (3.2 g in 150 ml) was added $NaBH_4$ (450 mg) in small portions and the mixture was stirred for 3 hr at room temperature. After evaporation of EtOH, the residue was treated with water and then extracted with ether. The ether solution was washed with water and dried over Na_2SO_4. Evaporation of the ether gave a crude product which was then chromatographed over silica gel to afford a viscous oil (**5l**, 1.8 g, 56%): ir ($CHCl_3$) 3600, 3400, 2950, 1675, 1600, 1495, 1365 cm^{-1}; nmr δ 2.60 (m, 2 H, 4-CH_2), 3.20 (broad, 1 H, –OH, the signal disappeared upon addition of a small amount of D_2O), 3.34 (m, 1 H, 5-CH), 3.72 (s, 3 H, $-OCH_3$), 4.40 (m, 2 H, 6-CH_2), 6.82 (s, 4 H, *p*-methoxyphenyl ring protons), 7.20–7.85 ppm (m, 5 H, phenyl protons); mass spectrum *m/e* 298 (M^+), 207, 176, 136, 135 (base peak), 123, 120, 93, 85.

To a solution of **5l** (1.8 g) in dry pyridine (80 ml), $POCl_3$ (1.0 g) was added dropwise and the mixture was stirred for 3 hr at room temperature. After evaporation of the pyridine under reduced pressure, the residual tar was treated with ice water and then extracted with ether. The ether solution was washed with 10% HCl and water and dried over Na_2SO_4. Evaporation of the ether followed by chromatography over silica gel gave **6l** as colorless needles (600 mg, 36%): mp 95°; ir ($CHCl_3$) 2950, 2840, 1665, 1620, 1600, 1495, 1380, 1300 cm^{-1}; nmr δ 3.68 (s, 3 H, $-OCH_3$), 4.34 (q, 2 H, J = 3 and 1 Hz, 6-CH_2), 6.08 (d, t, 1 H, J = 9 and 1 Hz, 4-CH=), 6.52 (d, t, 1 H, J = 9 and 3 Hz, 5-CH=), 6.82 and 6.87 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.10–7.85 ppm (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 224 nm (ϵ 6860), 285 (2000); mass spectrum *m/e* 280 (M^+, base peak), 212, 189, 188, 158, 135, 122, 107, 78, 77.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.85; H, 5.80; 9.89.

1-(4-Methoxyphenyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridazin-3-one (6o). Following the similar method described above, **2o** (2.5 g) was treated with $NaBH_4$ followed by dehydration with $POCl_3$ in dry pyridine to give **6o** (470 mg, 40%) as colorless needles: mp 102.5°; ir ($CHCl_3$) 3000, 2950, 2850, 1660, 1620, 1600, 1510, 1380, 1340, 1300, 1250 cm^{-1}; nmr δ 2.27 (s, 3 H, tolyl CH_3), 3.70 (s, 3 H, $-OCH_3$), 4.35 (q, 2 H, J = 3 and 1 Hz, 6-CH_2), 6.10 (d, t, 1 H, J = 9 and 1 Hz, 4-CH=), 6.50 (d, t, 1 H, J = 9 and 3 Hz, 5-CH=), 6.81 and 6.84 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.17 and 7.63 ppm (AB q, 4 H, J = 8 Hz, *p*-tolyl protons); uv λ_{max} (EtOH) 225 nm (ϵ 6700), 289 (2000); mass spectrum *m/e* 294 (M^+, base peak), 224, 201, 200, 174, 158, 149, 136, 121, 108, 93, 91, 77.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.54; H, 6.26; N, 9.32.

1-(4-Ethoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (6u). Following the above-cited method, **2u** (2.0 g) gave **6u** (400 mg, 42%) as pale yellow needles: mp 117°; ir ($CHCl_3$) 2980, 1662, 1615, 1595, 1480, 1380, 1340, 1295 cm^{-1}; nmr δ 1.32 (t, 3 H, J = 7 Hz, ethoxy CH_3), 3.89 (q, 2 H, J = 7 Hz, ethoxy CH_2), 4.32 (q, 2 H, J = 3 and 1 Hz, 6-CH_2), 6.14 (d, t, 1 H, J = 9 and 1 Hz, 4-CH=), 6.52 (d, t, 1 H, J = 9 and 3 Hz, 5-CH=), ~6.80 (overlapped d, 4 H, *p*-ethoxyphenyl protons), 7.16–7.85 ppm (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 225 nm (ϵ 6700), 289 (2000); mass spectrum *m/e* 294 (M^+), 226, 189, 188, 172, 135, 122, 107, 91 (base peak), 77.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 6.04; N, 9.30.

5-Acetoxy-1-(4-methoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (7l). To a solution of **2l** in dry pyridine (1.0 g in 50 ml), acetyl chloride (500 mg) was added dropwise and the mixture was stirred for 2 hr at room temperature. After evaporation of pyridine under reduced pressure, the residual oil was extracted with ether. The ether solution was washed with 5% NaOH, 10% HCl, and water, successively, and dried over Na_2SO_4. After evaporation of ether, the residual substance was chromatographed over silica gel followed by recrystallization from ethanol, giving **7l** (490 mg, 38%) as pale yellow needles: mp 86°; ir ($CHCl_3$) 3000, 1760, 1670, 1650, 1503, 1370, 1245, 1170, 1150 cm^{-1}; nmr δ 2.14 (s, 3 H, acetyl CH_3), 3.71 (s, 3 H, $-OCH_3$), 4.53 (s, 2 H, 6-CH_2), 6.03 (s, 1 H, 4-CH=), 6.83–6.85 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.05–7.83 ppm (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 236 nm (ϵ 10,000), 290 (4200); mass spectrum *m/e* 338 (M^+), 296, 247, 227, 205, 174, 136, 135 (base peak), 120, 107, 93, 77.

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.65; H, 5.31; N, 8.25.

5-Acetoxy-1-(4-ethoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (7u). Following the same method as mentioned above, **2u** (1.0 g) gave **7u** (680 mg, 60%) as colorless crystals: mp 129.5°; ir ($CHCl_3$) 2980, 1772, 1670, 1635, 1592, 1500, 1360, 1240, 1180, 1150 cm^{-1}; nmr δ 2.15 (s, 3 H, acetyl CH_3), 1.35 (t, 3 H,

J = 7 Hz, ethoxy CH_3), 3.94 (q, 2 H, J = 7 Hz, ethoxy CH_2), 4.54 (s, 2 H, 6-CH_2), 6.03 (s, 1 H, 4-CH=), 6.85 (overlapped d, 2 H and 2 H, p-ethoxyphenyl protons), 7.18–7.84 ppm (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 235 nm (ϵ 10,500), 290 (3550); mass spectrum m/e 352 (M^+), 310, 261, 242, 226, 219, 174, 150, 149, 148, 121 (base peak), 120, 93, 77.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.79; N, 7.87.

1-(4-Methoxyphenyl)-2-phenyl-5-(4-toluenesulfonyloxy)-1,2,3,6-tetrahydropyridazin-3-one (8l). To a solution of **2l** in dry pyridine (1.2 g in 70 ml), TsCl (1.3 g) was added in small portions, and the mixture was stirred for 2 hr at room temperature. After evaporation of pyridine under reduced pressure, the resulting residue was extracted with benzene. The benzene solution was washed with 5% NaOH, 10% HCl, and water, successively, and dried over Na_2SO_4. After evaporation of benzene, the residual solid was dissolved in $CHCl_3$ and chromatographed over silica gel, affording enol tosylate **8l** (850 mg, 47%) as colorless crystals: mp 117°; ir ($CHCl_3$) 3000, 1660, 1640, 1600, 1510, 1500, 1387, 1360, 1248, 1192, 1185 cm^{-1}; nmr δ 2.44 (s, 3 H, tolyl CH_3), 3.77 (s, 3 H, $-OCH_3$), 4.50 (s, 2 H, 6-CH_2), 5.75 (s, 1 H, 4-CH=), 6.84 (overlapped d, 4 H, p-methoxyphenyl protons), 7.24 and 7.60 (AB q, 2 H and 2 H, J = 7 Hz, p-tosyl protons), 7.14–7.82 (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 230 nm (ϵ 7100), 273 (3170); mass spectrum m/e 450 (M^+, base peak), 359, 328, 295, 225, 212, 162, 135, 120, 107, 91, 77.

Anal. Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.00; H, 5.04; N, 5.97.

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Registry No.—**1a,** 103-33-3; **1b,** 584-90-7; **1c,** 588-04-5; **1d,** 501-60-0; **1e,** 7334-33-0; **1f,** 15426-14-9; **1g,** 1602-00-2; **1h,** 613-55-8; **1i,** 6319-23-9; **1j,** 501-58-6; **1k,** 588-52-3; **1l,** 2396-60-3; **1m,** 29418-43-7; **1n,** 52148-10-4; **1o,** 29418-44-8; **1p,** 52148-11-5; **1q,** 52148-12-6; **1r,** 40473-79-8; **1s,** 24948-93-4; **1t,** 29418-59-5; **1u,** 7466-38-8; **2a,** 52148-13-7; **2b,** 52148-14-8; **2c,** 52148-15-9; **2d,** 52148-16-0; **2e,** 52148-17-1; **2f,** 52148-18-2; **2g,** 52148-19-3; **2h,** 52148-20-6; **2i,** 52148-21-7; **2j,** 52148-22-8; **2k,** 52148-23-9; **2l,** 52148-24-0; **2m,** 52148-25-1; **2n,** 52148-26-2; **2o,** 52148-27-3; **2p,** 52148-28-4; **2q,** 52148-29-5; **2r,** 52148-30-8; **2s,** 52148-31-9; **2t,** 52148-32-0; **2u,** 52148-33-1; **3a,** 52148-34-2; **3a′,** 52148-35-3; **4,** 52148-36-4; **5l,** 52148-37-5; **6l,** 52148-38-6; **6o,** 52148-39-7; **6u,** 52148-40-0; **7l,** 52148-41-1; **7u,** 52148-42-2; **8l,** 52148-43-3; diketene, 674-82-8; hydrazobenzene, 122-66-7; ω-bromoacetoacetyl bromide, 52148-44-4.

References and Notes

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Synthesis and Stereochemistry of Some 8-Substituted 2-Methyldecahydroisoquinolines

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The synthesis and assignment of stereochemistry of three of the four possible diastereoisomers of the previously unreported 8-amino-2-methyldecahydroisoquinolines is reported. A one-step hydrogenolysis–catalytic hydrogenation of 5-bromo-8-nitro-2-methylisoquinolium tosylate was used to prepare the isomeric 8-amino-2-methyldecahydroisoquinolines. Separation of the diastereoisomers was achieved by the fractional crystallization of the corresponding acetamide derivatives and allowed the separation of the cis-8,9,10-H (30%, IIIa), trans-8,9,10-H (65%, IIIb), and cis-9,10,trans-8,9-H (1%, IIIc) isomers. Deamination with nitrous acid of the amines (obtained by hydrolysis of the acetamides) to the corresponding hydroxy compounds confirmed the equatorial stereochemistry of the 8 substituent in IIIb and IIIc. In the case of the amine obtained from IIIa, which possesses an intramolecular hydrogen bond and of necessity an axial substituent, high yields of the corresponding axial hydroxy compound were obtained on deamination. Owing to a conformational equilibrium this finding is not in conflict with the established high-yield conversions of equatorial amines to alcohols using nitrous acid. The isolation of alcohol IVc, as its methiodide derivative, completes the description of the four possible diastereoisomers of 8-hydroxy-2-methyldecahydroisoquinoline.

In a continuing study of the involvement of stereochemistry in the cardiovascular potencies of various derivatives of amino and hydroxy substituted decahydroisoquinolines[1] we report on the stereochemistry of 8-amino- and 8-hydroxy-2-methyldecahydroisoquinolines. Studies have been reported by Kimoto and Okamoto[2] on some 8-hydroxy-2-methyldecahydroisoquinolines; however, in comparing some of the melting point data with the present data, discrepancies are apparent. Elucidation of the conformation of the previously unreported 8-amino analogs is described.

The synthesis of 8-nitroisoquinoline (see Scheme I) was achieved by way of the bromination of isoquinoline using a swamping catalyst technique[3] to yield 5-bromoisoquinoline. Nitration using standard procedures gave good yields of the 5-bromo-8-nitroisoquinoline which was quaternized with methyl p-toluenesulfonate. The resulting salt (I) was then subjected to sequential reductions to produce the desired decahydroisoquinoline. The dehydrohalogenation of heterocycles is well documented[3] and using a base-supported palladium catalyst in addition to platinum oxide we

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