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Cyclic Guanidines. V.[1] Synthesis of Hypoglycemic 2,2- and 3,3-Diphenylimidazo[1,2-*a*][1,3]-diazacycloalkane Derivatives[2]

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Synthesis of 2,2- and 3,3-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives (**4**) and (**5**) was attempted. The cyclization of 2-(ω-chloroalkylimino)-4,4-diphenylimidazolidines (**3**) was not advantageous because it gave a mixture of **4** and **5** in low yield. 5,5-Diphenylhydantoin (**6**) was alkylated at the N_3 or O_2 position and successive reduction of the remained carbonyl group of the products resulted in success. The 3-N-alkylated compounds (**14**) prepared from **6** selectively gave **4**. The 2-O-ethyl derivative (**19**) afforded 2-(ω-chloroalkylimino)derivatives (**21**). Heating **21** gave 2-oxo-bicyclic guanidines (**22**), and treatment of **21** with sodium hydride yielded 3-oxo-bicyclic guanidines (**17**) in good yield, respectively. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of **17** and **22**, having a carbonyl group in the molecule, gave **4** and **5**, respectively. Under the same conditions, N-methyl-2-oxo- or 3-oxo-bicyclic guanidines (**18**) and (**28**) gave partially reduced products.

The bicyclic guanidines (**4**) and (**5**) showed potent hypoglycemic activity.

Keywords——diphenylhydantoin derivative; imidazo[1,2-*a*][1,3]diazacycloalkane; imidazo[1,2-*a*][1,3]diazacycloalkanone; 9-oxo-1,6-diazabicyclo[4,2,1]nonane; alkylation; intramolecular cyclization; reduction of acyl guanidine; Meerwein reagent; hypoglycemic activity

The previous papers[1,4] described synthesis and hypoglycemic activity of the cyclic guanidines. Among the cyclic guanidines tested, N-benzhydryl bicyclic guanidine derivatives showed the most effective hypoglycemic activity.[1] The synthesis of the cyclic guanidines

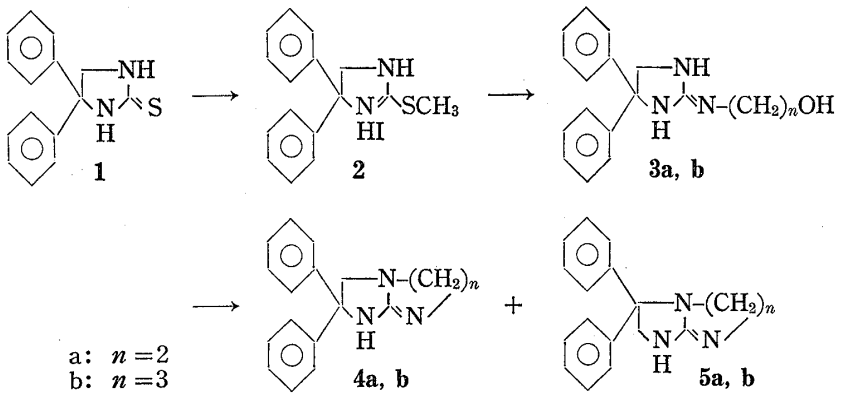
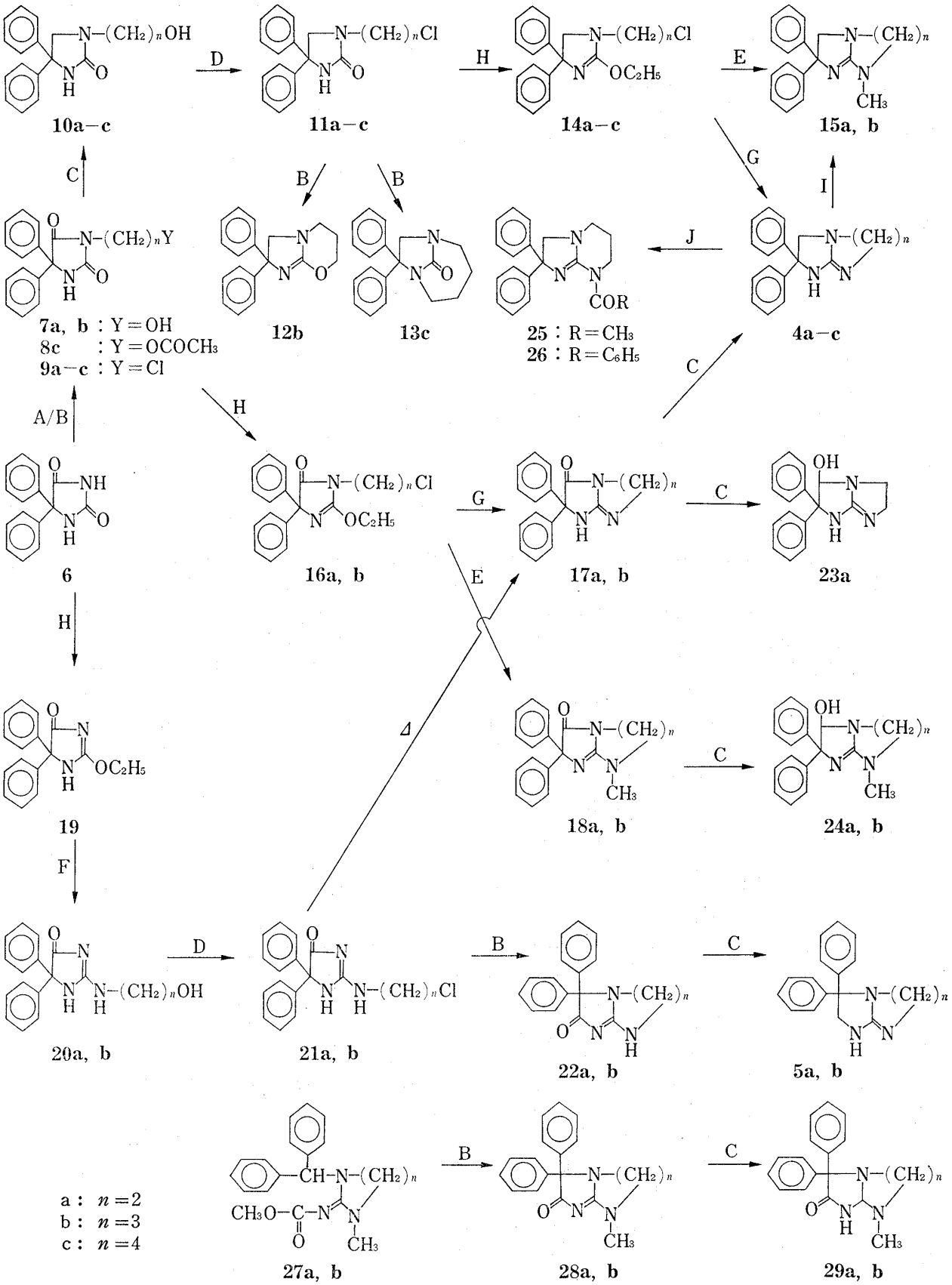


Chart 1

1) Part IV: A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 841 (1979).
2) This work was presented at 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
4) *a*) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3658 (1978); *b*) F. Ishikawa, A. Kosasayama, and T. Konno, *ibid.*, **26**, 3666 (1978); *c*) A. Kosasayama, Y. Watanabe, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 831 (1979).



A=X-$(CH_2)_n$-Y (X=Br, Cl; Y=Cl, OH, $OCOCH_3$), B=NaH, C=$NaAlH_2(OCH_2CH_2OCH_3)_2$, D=$SOCl_2$, E=$CH_3NH_2$, F=$HO(CH_2)_nNH_2$, G=$NH_3$, H=$(C_2H_5)_3OBF_4$, I=$CH_3I$, J=RCOCl (R=$CH_3$, C_6H_5).

Chart 2

which were substituted with geminal diphenyl group at the methylene carbon in the molecule is interesting from the viewpoint of structure–activity relationships. This paper describes new observations containing the synthesis and hypoglycemic activity of 2,2- and 3,3-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives.

4,4-Diphenylimidazolin-2-thione (**1**) obtained by the method of Marshall[5] was methylated with methyl iodide to yield 2-methylthio derivative (**2**). When **2** was heated with 2-aminoethanol or 3-aminopropanol in ethanol, 4,4-diphenyl-2-(ω-hydroxyalkylimino)imidazolidines (**3a,b**) were obtained in good yields. The chlorination of **3a** with thionyl chloride followed by cyclization upon treatment with methanolic potassium hydroxide resulted in the formation of the mixture of 2,2-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (**4a**) and 3,3-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (**5a**) in 3% and 29% yields, respectively. Analogously, **3b** gave the mixture of 2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (**4b**) and 3,3-diphenyl derivative (**5b**) in 22% and 18% yields, respectively. The structures of **4** and **5** were confirmed by identification with the samples prepared by the certain methods described below.

Although **4** and **5** were obtained by the cyclization of **3**, this reaction was not practical because the isolation of products was troublesome. Some methods for the certain and practical synthesis of **4** and **5** have been researched. 5,5-Diphenylhydantoin (**6**), a starting material, was alkylated at the N_3 or O_2 position and then reduction of the remained carbonyl group of the products resulted in success.

First, synthesis of 2,2-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives was investigated. Previously, it has been confirmed that alkylation of **6** with alkyl halides in the presence of base resulted in the formation of 3-alkyl derivatives.[6] Thus, heating **6** with halohydrine such as ethylenebromohydrine or propylenechlorohydrine in the presence of sodium hydride in dimethylformamide (DMF) afforded 5,5-diphenyl-3-(ω-hydroxyalkyl)-hydantoin (**7a**)[7] and (**7b**). Analogously, reaction of **6** with 4-chlorobutyl acetate gave 3-(4-acetoxybutyl)-5,5-diphenylhydantoin (**8c**). According to the Driscoll's procedure,[7] sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al) reduction of **7** and **8** in tetrahydrofuran (THF) gave predominantly 1-substituted 4,4-diphenyl-2-imidazolinones (**10a—c**). When **10a—c** were treated with thionyl chloride at room temperature for several hours, **10a** afforded 1-(2-chloroethyl) derivative (**11a**) in good yield. In the case of **10b** and **10c**, similar chlorination gave the corresponding chlorides (**11b, c**) together with by-products (**12b** and **13c**). The by-products (**12b** and **13c**) were also formed upon treatment of **11b** and **11c** with sodium hydride in good yields, respectively.

Elemental analysis and mass spectrum of **12b** established the molecular formula $C_{18}H_{18}N_2O$. Its infrared (IR) spectrum exhibited a strong absorption at 1620 cm^{-1} assignable to the C=N stretching band. The nuclear magnetic resonance (NMR) spectrum of **12b** showed a triplet signal at δ 4.18 assignable to the methylene hydrogens adjacent to the oxygen. These spectral data supported the structure of 7,7-diphenyl-1,2,3,4,6,7-hexahydroimidazo-[2,1-*b*][1,3]oxazine. Mass spectral and elemental analysis of **13c** established the molecular formula $C_{19}H_{20}N_2O$. The IR spectrum of **13c** showed a carbonyl band at 1745 cm^{-1} which is characteristic of 1,3-butano-2-imidazolidinone.[8] The NMR signal at δ 3.06 (four protons, multiplet) can be assigned to methylene hydrogens adjacent to nitrogen. Thus, the structure of **13c** was confirmed to be 9-oxo-7,7-diphenyl-1,6-diazabicyclo[4,2,1]nonane.

Treatment of **11a—c** with Meerwein reagent in methylene chloride gave oily 2-ethoxy derivatives (**14a—c**), which can be used to the subsequent reaction without further purification.

5) F. Marshall, *J. Am. Chem. Soc.*, **78**, 3936 (1956).
6) K. Schoegl, F. Wessely, O. Kraupp, and H. Stormann, *J. Med. Chem.*, **4**, 231 (1961).
7) V.E. Marquez, L. Twanmoh, H.B. Wood, Jr. and J.S. Driscoll, *J. Org. Chem.*, **37**, 2558 (1961).
8) R.J. Hayward and O. Meth-Cohn, *J. Chem. Soc. Perkin I*, **1975**, 219.

When **14a**—**c** were heated with ethanolic ammonia in a sealed tube, final products, 2,2-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives (**4a**—**c**), were obtained. Also heating **14a, b** with methylamine in aqueous ethanol gave corresponding 7- or 8-methyl derivatives (**15a** and **15b**), respectively. In these cyclization, six-membered ring was formed more smoothly than five-membered ring.

Reaction of diphenylhydantoin (**6**) with alkylene dihalide in the presence of sodium hydride in DMF gave 3-(ω-chloroalkyl) derivatives (**9a**—**c**) which were treated with Meerwein reagent to yield 2-ethoxy derivatives (**16a, b**). The compounds **16a, b** were heated in ethanolic ammonia in a sealed tube or methylamine in aqueous ethanol to give bicyclic products **17** and **18**, respectively.

Reaction of **6** with Meerwein reagent in methylene chloride gave only 2-ethoxy-5,5-diphenyl-2-imidazolin-4-one (**19**). The structure of **19** was confirmed by the fact of the formation of **17** and **22** *via* **19** and **21** as described below. If the ethylation of **6** with Meerwein reagent occurred at C_4 oxygen, such results are unable to explain. Compound **19** was heated with 2-aminoethanol or 3-aminopropanol in ethanol to give 2-(ω-hydroxyalkyl) derivatives (**20a, b**) in good yields. Heating **20a, b** in thionyl chloride gave 2-(ω-chloroalkyl) derivatives (**21a, b**) in quantitative yield. On the successive cyclization of **21a, b**, interesting reactions were observed. When **21a, b** were treated with sodium hydride in DMF at room temperature, 2-oxo-3,3-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives (**22a, b**) were obtained in quantitative yield. On the other hand, heating **21a, b** at 200° yielded predominantly 3-oxo-2,2-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives (**17a, b**) which were identical with the samples obtained from **16a, b**.

Red–Al reduction of the carbonyl group of bicyclic guanidine derivatives (**17**, **18**, **22** and **28**) was attempted and the results are shown in Table III.

Lithium aluminum hydride reduction of acyl guanidines has been recently reported by Rapoport and co-worker.[9] They demonstrated that the monoacyl guanidines possessing at least one hydrogen atom at the guanidine nitrogen can be reduced to corresponding alkyl guanidines and fully substituted monoacyl guanidines involving the structure of acyl-imino type gave some degradation products by the reduction at the acyl-imino double bond (Acyl–N=C–).

It was expected that the acyl group of **17** and **22** was reduced to methylene group because these compounds have one hydrogen at the nitrogen. Heating **17b** and **22** with excess of Red–Al in THF for several hours gave smoothly the desired compounds **4b** and **5a, b** in satisfactory yields. However, under similar conditions, reduction of **17a** gave partially reduced compound, 3-hydroxy derivative (**23a**), in good yield. The IR spectrum of **23a** showed an absorption band at 3290 cm^{-1} attributed to hydroxy group. The NMR signals were presented at δ 5.47 (broad singlet for the hydroxy hydrogen at C_3). The mass spectrum of **23a** presented a molecular ion peak at *m/e* 279. In order to prepare **4a** from **17a**, a large excess of Red–Al and prolonged reaction time were necessary. Thus, a practical preparative method of the desired compounds **4** and **5** was established and these compounds were identical with the samples obtained from **3**, respectively.

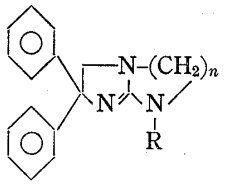
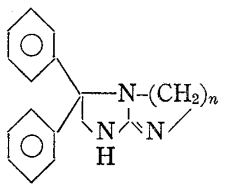
The reduction of fully alkylated acyl guanidines (**18**) having acyl–imino structure with Red–Al is of interest because Rapoport[9] did not mentioned about the reduction of this kind of acyl guanidines. Reaction of **18a** with excess of Red–Al in THF afforded a partially reduced 3-hydroxy derivative (**24a**). The structure of **24a** was confirmed on the basis of spectral data [IR band at 1650 cm^{-1} attributed to the C=N streching, NMR signals at δ 5.44 (singlet for the methine proton at C_3) and 5.78 (singlet for the hydroxy hydrogen at C_3), and mass spectrum at *m/e* 293 (molecular ion) and 275 (base peak, due to the loss of H_2O)]. In the same procedure, **18b** gave a similar product (**24b**).

9) J.F. Steans and H. Rapoport, *J. Org. Chem.*, **42**, 3608 (1977).

In a sharp contrast, reduction of 7- or 8-methylated 2-oxo-3,3-diphenylimidazo[1,2-*a*]-[1,3]diazacycloalkane derivatives (**28a, b**),[4b] fully alkylated acylimino type guanidines, resulted in the reduction of the C=N double bond in agreement with Rapoport's observation. Heating **28a** with excess of Red–Al in THF for several hours gave perhydro bicyclic guanidine, 2-oxo-3,3-diphenyl-2,3,5,6,7,7a-hexahydro-1H-imidazo[1,2-*a*]imidazole (**29a**). The structure of **29a** was confirmed on basis of spectral data [IR band at 1690 cm^{-1} attributed to the C=O stretching, NMR signal at δ 5.20 corresponding to the methine proton at C_{7a}, and mass spectrum at *m/e* 293 due to the molecular ion]. The same reduction of **28b** gave a similar compound **29b** in good yield.

Treatment of **4b** with methyl iodide and sodium hydride in DMF gave 8-methylated derivative (**15b**) in 50% yield, which was identical with a sample prepared from **14b**. Acetylation of **4b** with acetyl chloride in chloroform afforded 8-acetylated compound **25**. The IR spectrum of **25** exhibited absorptions at 1670 cm^{-1} (C=O) and 1610 cm^{-1} (C=N). The NMR signals showed at δ 3.13 (methylene protons at C_5) and 3.76 (methylene protons at C_7). The latter signal was shifted 0.6—0.7 ppm to lower field as compared with that of starting material (**4b**). Benzoylation of **4b** with benzoyl chloride under the same conditions gave a similar product (**26**).

Table I. Hypoglycemic Activity of 2,2- and 3,3-Diphenylimidazo-[1,2-*a*][1,3]diazacycloalkane Derivatives

Compound[a]	Plasma glucose[b]	
	Dosage (mg/kg, *p.o.*)	% reduction
	25	20—40
	25	30—40

a) R=H, CH_3, $COCH_3$, COC_6H_5; n=2—4.
b) Test compound was orally administrated to rats which had been fasted overnight. Plasma glucose was determined by the glucose oxidase method at 2—5 hr after the administration.

Most of the geminal diphenyl substituted bicyclic guanidines described above have hypoglycemic activity in fasted rats. Some of these results are shown in Table I. The structure–activity relationships in a series of the cyclic guanidines will be elsewhere in detail.

Experimental

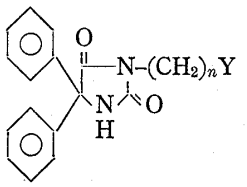
All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. Mass spectra (MS) were determined on a JEOL 01SG-2 MS spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2-Methylthio-4,4-diphenyl-2-imidazoline (2)——A mixture of 9.50 g (37 mmol) of 4,4-diphenylimidazolidin-2-thione[5] (**1**) and 5.80 g (41 mmol) of MeI in 75 ml of EtOH was refluxed for 2 hr. After cooling, the solution was evaporated to half volume *in vacuo* and ether was added to the residual solution. Colorless solid was collected to yield 11.1 g (75%) of **2**, mp 209—215°. IR ν_{max}^{KBr} cm^{-1}: 3050, 2870, 1540, 1520. *Anal.* Calcd. for $C_{16}H_{17}IN_2S$: C, 48.49; H, 4.32; N, 7.07. Found: C, 48.30; H, 4.44; N, 7.16.

2-(2-Hydroxyethylimino)-4,4-diphenylimidazolidine (**3a**)——A mixture of 3.96 g (10 mmol) of **2** and 1.20 g of 2-aminoethanol in 40 ml of EtOH was refluxed for 12 hr and concentrated to dryness *in vacuo*. The residue was mixed with 2 N NaOH. A solid was collected to yield 2.20 g (78%) of **3a**, mp 167—168° (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 3360, 1610, 1570. *Anal.* Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.84; H, 7.01; N, 13.97.

2-(3-Hydroxypropylimino)-4,4-diphenylimidazolidine (**3b**)——Compound **2** (8.00 g 20 mmol) was treated with 3.0 g of 3-aminopropanol as described in the synthesis of **3a** to give 4.01 g (68%) of **3b**, 116—118° (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 3300, 1675, 1610, 1580. *Anal.* Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.07; H, 7.20; N, 14.24.

Table II. 3-Substituted 5,5-Diphenylhydantoin Derivatives (**7**, **8**, and **9**)



No.	*n*	Y	Reaction condition: Reagent	Temp. (°C)	Time (hr)	Yield (%)	mp[a] (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found): C	H	N
7a[6]	2	OH	$Br(CH_2)_2OH$	25	3	81	180—182	1765 1700	$C_{17}H_{16}N_2O_3$	68.90 (68.50	5.44 5.40	9.45 9.73)
7b	3	OH	$Cl(CH_2)_3OH$	100	1	64	112—114	1780 1695	$C_{18}H_{18}N_2O_3$	69.66 (69.41	5.85 5.85	9.03 9.12)
8c	4	$OCOCH_3$	$Cl(CH_2)_4OCOCH_3$	100	2.5	86	111—114	1765 1725 1705	$C_{21}H_{22}N_2O_4$	68.83 (69.02	6.05 6.01	7.65 7.47)
9a	2	Cl	$Br(CH_2)_2Cl$	80	0.5	95	151—152	1775 1715	$C_{17}H_{15}ClN_2O_2$	64.87 (64.99	4.80 4.74	8.90 9.18)
9b	3	Cl	$Cl(CH_2)_3Cl$	100	1	85	148—159	1760 1695	$C_{18}H_{17}ClN_2O_2$	65.75 (65.57	5.21 5.15	8.52 8.51)

a) All compounds were recrystallized from benzene or benzene–acetone.

3-(2-Hydroxyethyl)-5,5-diphenylhydantoin (**7a**)[6]——A mixture of 25.2 g (0.1 mol) of diphenylhydantoin (**6**) and 6.00 g (0.126 mol) of NaH (50% oil suspension) in 500 ml of DMF was stirred at 50—60° for 30 min. After cooling, to the mixture was added 25.0 g (0.2 mol) of ethylenebromohydrine and the mixture was further stirred at room temperature for 3 hr. The reaction mixture was poured into 1.5 l of water and a solid was collected to yield 24.1 g (81%) of **7a**.

Other 3-substituted 5,5-diphenylhydantoins (**7b**, **8c** and **9a**, **b**) were prepared by a method similar to that described above and are shown in Table II along the alkylating reagents and the reaction conditions.

1-(3-Hydroxypropyl)-4,4-diphenyl-2-imidazolidinone (**10b**)——Following a method similar to that described by Driscoll,[7] to the mixture of 19.6 g (63.5 mmol) of **7b** in 400 ml of THF was slowly added 126 ml of Red-Al (70% benzene solution) with stirring. The mixture was worked up as usual to give 11.0 g (56%) of **10b**, mp 141—143° (from acetone–ether). IR ν_{max}^{KBr} cm^{-1}: 3420, 3220, 1670, 1380. *Anal.* Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.11; H, 6.81; N, 9.35.

1-(4-Hydroxybutyl)-4,4-diphenyl-2-imidazolidinone (**10c**)——Compound **8c** (13.8 g, 38 mmol) was treated with 75 ml of Red-Al (70% benzene solution) in THF as described in the preparation of **10b** to give 6.60 g (56%) of **10c**, mp 74—75° (from acetone–ether). IR ν_{max}^{KBr} cm^{-1}: 3350, 1685, 1385. *Anal.* Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.51; H, 7.14; N, 9.03. Found: C, 73.86; H, 7.00; N, 8.88.

1-(2-Chloroethyl)-4,4-diphenyl-2-imidazolidine (**11a**)——To 20 ml of $SOCl_2$ was added portionweise 3.70 g (13 mmol) of **10a**[7] at 5—10°. The mixture was allowed to stand at room temperature for 2 hr. Excess of $SOCl_2$ was removed *in vacuo* and the residue was recrystallized from acetone–ether to yield 3.50 g (90%) of **11a**, mp 146—148°. IR ν_{max}^{KBr} cm^{-1}: 3200, 3050, 1690, 1470. *Anal.* Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 8.31. Found: C, 68.02; H, 5.75; N, 8.57.

1-(3-Chloropropyl)-4,4-diphenyl-2-imidazolidinone (**11b**)——Following a similar procedure for the synthesis of **11a**, 5.00 g (16.9 mmol) of **10b** was treated with 34 ml of $SOCl_2$. After removal of $SOCl_2$, the residue was dissolved in $CHCl_3$ and the solution was washed with 20 ml of 1 N HCl. The organic layer was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from ether

to give 3.30 g (62%) of **11b**, mp 114—116. IR ν_{max}^{KBr} cm^{-1}: 3200, 3060, 2850, 1680. *Anal.* Calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.59; H, 6.02; N, 8.01.

The washing with 1 N HCl was made basic with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from acetone to yield 0.80 g (17%) of **12b**, mp 216—218°, which was identical with a sample prepared from **11b** and NaH.

1-(4-Chlorobutyl)-4,4-diphenyl-2-imidazolidinone (11c)——Following a similar procedure for the synthesis for **11b**, 6.50 g (21 mmol) of **10c** was treated with 50 ml of $SOCl_2$. After removal of $SOCl_2$, the $CHCl_3$ solution of the residue was washed with 1 N HCl and evaporated to yield 4.30 g (62%) of **11c**, mp 91—92° (from ether). IR ν_{max}^{KBr} cm^{-1}: 3170, 3060, 1690. *Anal.* Calcd. for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 69.35; H, 6.35; N, 8.68.

The washing with 1 N HCl was made basic with 2 N NaOH and extracted with $CHCl_3$. The solvent was removed *in vacuo* to give 0.45 g (7%) of **13c**, mp 166—168° (from acetone), which was identical with a sample prepared from **11c** and NaH.

7,7-Diphenyl-3,4,6,7-tetrahydro-2H-imidazo[2,1-*b*]oxazine (12b)——A mixture of 3.15 g (10 mmol) of **11b** and 0.96 g of NaH (50% oil suspension) in 30 ml of DMF was stirred at room temperature for 2 hr. The mixture was poured into ice-water and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from acetone to yield 2.20 g (80%) of **12b**, mp 217—218°. IR ν_{max}^{KBr} cm^{-1}: 2840, 1620. NMR ($CDCl_3$) δ: 4.18 (2H, t, J=7 Hz, C_2–CH_2), 3.94 (2H, s, C_6–CH_2), 3.12 (2H, t, J=7 Hz, C_4–CH_2), 1.96 (2H, m, C_3–CH_2). MS *m/e*: 278 (M^+). *Anal.* Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.62; H, 6.56; N, 9.64.

9-Oxo-7,7-diphenyl-1,6-diazabicyclo[4,2,1]nonane (13c)——Following a similar procedure for the synthesis of **12b**, 3.30 g (10 mmol) of **11c** was treated with 0.96 g of NaH (50% oil suspension) to give 1.80 g (62%) of **13c**, mp 167—168° (from acetone). IR ν_{max}^{KBr} cm^{-1}: 1745, 1445. NMR ($CDCl_3$) δ: 3.82 (2H, s, C_3–CH_2), 3.06 (4H, m, C_5– and C_8–CH_2), 1.92 (4H, m, C_6– and C_7–CH_2). MS *m/e*: 291 (M^+−1), 243 (M−43, base peak). *Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.98; H, 6.89; N, 9.71.

1-(2-Chloroethyl)-2-ethoxy-4,4-diphenyl-2-imidazoline (14a)——To a solution of 2.30 g (12 mmol) of Et_3OBF_4 (Meerwein reagent) in 50 ml of CH_2Cl_2 was added 3.00 g (10 mmol) of **11a**. The mixture was stirred at room temperature for 3 hr. The mixture was poured into 200 ml of 10% Na_2CO_3 solution and organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined, washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to yield 3.01 g (92%) of **14a** as oil, which was used without further purification. NMR ($CDCl_3$) δ: 4.40 (2H, q, J=7 Hz, O–CH_2), 4.00 (2H, s, C_5–CH_2), 3.50 (4H, m, N–CH_2CH_2Cl), 1.32 (3H, t, CH_3).

1-(3-Chloropropyl)-2-ethoxy-4,4-diphenyl-2-imidazoline (14b)——Compound **11b** (2.60 g, 8.4 mmol) was treated with 2.10 g of Et_3OBF_4 as described in the synthesis of **14a** to yield 1.70 g (57%) of **14b** as oil. NMR ($CDCl_3$) δ: 4.38 (2H, q, J=7 Hz, O–CH_2) 3.90 (2H, s, C_5–CH_2), 3.47, 3.20 (2H, 2, t, J=7 Hz, N–CH_2 and Cl–CH_2), 1.80 (2H, m, C–CH_2–C), 1.30 (3H, t, CH_3).

1-(4-Chlorobutyl)-2-ethoxy-4,4-diphenyl-2-imidazoline (14c)——Compound **11c** (3.44 g, 10.5 mmol) was treated with 2.7 g of Et_3OBF_4 as described in the synthesis of **14a** to yield 2.30 g (62%) of **14c** as oil. NMR ($CHCl_3$) δ: 4.40 (2H, q, J=7 Hz, O–CH_2), 3.89 (2H, s, C_5–CH_2), 3.49, 3.07 (2H 2, t, J=7 Hz, N–CH_2 and Cl–CH_2), 1.67 (2H, m, C–CH_2CH_2–C), 1.32 (3H, t, CH_3).

1-(2-Chloroethyl)-2-ethoxy-4,4-diphenyl-2-imidazolin-5-one (16a)——To a solution of 12 g of Et_3OBF_4 in 80 ml of CH_2Cl_2 was added 6.28 g (20 mmol) of **9a**. The mixture was refluxed for 4 hr. After cooling, the mixture was poured into 10% Na_2CO_3 solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to yield 5.80 g (86%) of **16a**. mp 106—108° (from acetone–ether). IR ν_{max}^{KBr} cm^{-1}: 1740, 1655. *Anal.* Calcd. for $C_{19}H_{19}ClN_2O_2$: C, 66.56; H, 5.59; N, 8.17. Found: C, 66.30; H, 5.38; N, 8.18.

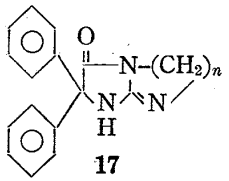
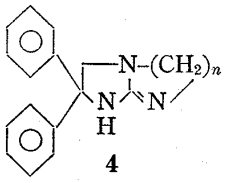
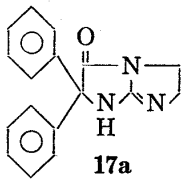
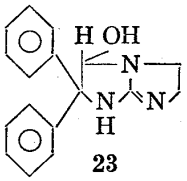
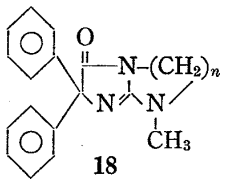
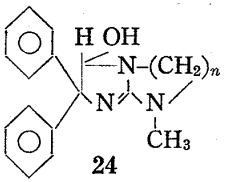
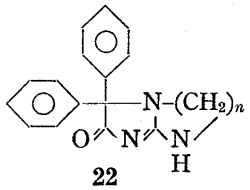
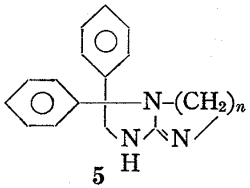
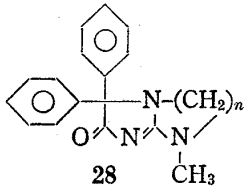
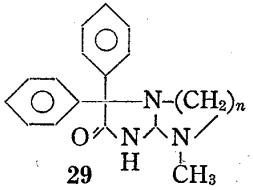
1-(3-Chloropropyl)-2-ethoxy-4,4-diphenyl-2-imidazolin-5-one (16b)——Compound **9b** (2.10 g, 6.5 mmol) was treated with 4.0 g of Et_3OBF_4 as described in the synthesis of **16a** to yield 1.80 g (78%) of **16b**, mp 83—84° (from acetone–ether). IR ν_{max}^{KBr} cm^{-1}: 1735, 1635. *Anal.* Calcd. for $C_{20}H_{21}ClN_2O_2$: C, 67.31; H, 5.93; N, 7.85. Found: C, 66.97; H, 5.81; H, 7.85.

3-Oxo-2,2-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (17a)——a) Compound **16a** (1.70 g, 5 mmol) was added to 50 ml of 10% NH_3–MeOH solution and the mixture was heated at 120° for 10 hr in a sealed tube. After cooling, the mixture was concentrated *in vacuo* and the residue was treated with water and ether. A solid was collected to yield 0.36 g (26%) of **17a**, mp 251—254° (from $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1730, 1685. *Anal.* Calcd. for $C_{17}H_{15}N_3O$: C, 73.62; H, 5.45; N, 15.15. Found: C, 73.52; H, 5.49; N, 15.42.

b) Compound **21a** (1.29 g, 3.8 mmol) was heated at 190—200° for 10 min. After cooling, the reaction residue was dissolved in small amounts of MeOH and the solution was poured into 5% $NaHCO_3$ solution. An insoluble solid was collected and recrystallized from acetone to give 0.92 g (88%) of **17a**.

3-Oxo-2,2-diphenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]pyrimidine (17b)——a) Compound **16b** (0.70 g, 2.0 mmol) was treated with 10% NH_3–MeOH solution as described in a method a) for the synthesis of **17a** to give 0.38 g (67%) of **17b**, mp 254—257° (from $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1720, 1675. *Anal.* Calcd. for $C_{18}H_{17}N_3O \cdot 2H_2O$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.43; H, 6.59; N, 12.98.

TABLE III. Sodium Bis(methoxyethoxy)aluminium Hydride Reductions of Oxo Bicyclic Guanidine Derivatives (**17**, **18**, **22**, and **28**)

Starting material	n	Reaction Red-Al (mol. eq.)	Condition time (hr)	Product	Yield (%)	mp (°C) (Recryst. Solv.)	IR (cm^{-1})	NMR (δ)[a] (Solv.)	Formula	Analysis Calcd. (Found) C	H	N
 **17**	2	12.5	9	 **4**	29	204—206 (AcOEt)	1675	3.72 (C)	$C_{17}H_{17}N_3$	77.54 (77.24	6.51 6.53	15.96 16.02)
	3	5	1.5		81	227—228 (AcOEt)	1650	3.79 (C)	$C_{18}H_{19}N_3$	77.95 (78.04	6.90 6.95	15.15 15.10)
 **17a**	2	5	3	 **23**	93	179—180 (AcOEt)	1655	5.47 (D)	$C_{17}H_{17}N_3O$	73.09 (73.26	6.13 6.23	15.04 15.13)
 **18**	2	5	3	 **24**	75	215—217 (AcOEt)	1650	5.44 (D)	$C_{18}H_{19}N_3O$	73.69 (74.07	6.53 6.62	14.32 14.46)
	3	5	3		80	182—184 (AcOEt)	1594	5.33 (D)	$C_{19}H_{21}N_3O$	74.24 (73.92	6.89 6.87	13.67 13.91)
 **22**	2	4	1.5	 **5**	57	244—245 (AcOEt)	1665	4.41 (C)	$C_{17}H_{17}N_3$	77.54 (77.43	6.51 6.53	15.96 15.92)
	3	5	3		62	212—214 (AcOEt)	1660	4.04 (C)	$C_{18}H_{19}N_3$	77.95 (78.08	6.90 6.94	15.15 15.17)
 **28**	2	5	4	 **29**	86	158—160 (Benzene)	1685	5.15 (C)	$C_{18}H_{19}N_3O$	73.69 (73.40	6.53 6.43	14.32 13.91)
	3	5	5		85	149—151 (Benzene)	1710	4.42 (C)	$C_{19}H_{21}N_3O$	74.24 (74.37	6.89 6.86	13.67 13.47)

a) Chemical shift of the methylene or methine proton at C_2, C_3, C_{7a} or C_{8a}. C=$CDCl_3$. D=d_6-DMSO.

b) Compound **21b** (3.27 g, 10 mmol) was heated at 200° for 10 min as described in a method b) for the synthesis of **17a** to yield 2.60 g (90%) of **17b**.

7-Methyl-3-oxo-2,2-diphenyl-2,3,5,6-tetrahydro-7H-imidazo[1,2-*a*]imidazole (18a)——A mixture of 2.00 g (5.8 mmol) of **16a**, 20 ml of 20% aqueous $MeNH_2$ solution and 20 ml of EtOH was refluxed for 22 hr. The mixture was concentrated *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g) and the fraction eluted with $CHCl_3$–MeOH was collected. From the second fraction, 1.00 g (59%) of **18a** was obtained, mp 174—176° (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1720, 1685. *Anal.* Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 73.82; H, 5.93; N, 14.56.

8-Methyl-3-oxo-2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (18b)——Compound **16b** (3.60 g, 10 mmol) was treated with $MeNH_2$ in aqueous MeOH as described in the synthesis of **18a** to give 1.50 g (49%) of **18b**, mp 165—167° (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1735, 1640. *Anal.* Calcd. for $C_{19}H_{10}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.68; H, 6.27; N, 14.06.

2-Ethoxy-5,5-dipheny-2-imidazolin-4-one (19)——A mixture of 6.25 g (25 mmol) of **6** and 9.6 g of Et_3OBF_4 in 250 ml of CH_2Cl_2 was refluxed overnight. The mixture was poured into 300 ml of 5% $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was recrystallized from AcOEt to yield 6.10 g (88%) of **19**, mp 186—187°. IR ν_{max}^{KBr} cm^{-1}: 1690, 1580, 1560. NMR ($CDCl_3$) δ: 7.30 (10H, s, aromatic protons), 4.54 (2H, q, J=7 Hz, O–CH_2), 1.33 (3H, t, CH_3). *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.94; H, 5.75; N, 9.98.

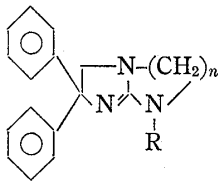
2-(2-Hydroxyethyl)-5,5-diphenyl-2-imidazolin-4-one (20a)——A mixture of 2.20 g (8 mmol) of **19** and 1.00 g of 2-aminoethanol in 40 ml of EtOH was refluxed for 2 hr. After cooling, a solid was collected to give 2.01 g (85%) of **20a**, mp>280° (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1680, 1635. *Anal.* Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.18; H, 5.77; N, 13.97.

2-(3-Hydroxypropyl)-5,5-diphenyl-2-imidazolin-4-one (20b)——Compound **19** (2.80 g, 10 mmol) was treated with 1.50 g of 3-aminopropanol in 40 ml of EtOH as decribed in the synthesis of **20a** to yield 2.62 g (88%) of **20b**, mp 219—220° (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1680, 1620. *Anal.* Calcd. for $C_{18}H_{19}N_3O$: C, 69.87; H, 6.19; N, 13.58. Found: C, 70.07; H, 6.22; N, 13.87.

2-(2-Chloroethyl)-5,5-diphenyl-2-imidazolin-4-one (21a)——A solution of 1.30 g (4.4 mmol) of **20a** in 10 ml of $SOCl_2$ was refluxed for 20 min and concentrated *in vacuo*. The residue was dissolved in small amounts of MeOH and the solution was poured into 5% $NaHCO_3$ solution. An insoluble solid was collected to give 1.30 g (94%) of **21a**, mp 165—166° (from $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1700, 1625, 1520. *Anal.* Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.12; H, 5.13; N, 13.69.

2-(3-Chloropropyl)-5,5-diphenyl-2-imidazolin-4-one (21b)——Compound **20b** (2.16 g, 7 mmol) was treated with 15 ml of $SOCl_2$ as described in the synthesis of **21a** to give 2.20 g (97%) of **21b**, mp 149—150° (from $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1695, 1625, 1520. *Anal.* Calcd. for $C_{18}H_{18}ClN_3O$: C, 65.93; H, 5.54; N, 12.82. Found: C, 65.66; H, 5.41; N, 12.60.

TABLE IV. Reaction Products of 1-(ω-Chloroalkyl)-2-ethoxy-4,4-diphenyl-2-imidazolines (**14a—c**) with Amines



No.	R	*n*	Yield (%)	mp (°C) (Recryst. Solv.)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
4a[a]	H	2	29						
4b[a]	H	3	77						
4c	H	4	35	163—164 (AcOEt)	1640	$C_{19}H_{21}N_3$	78.32 (78.01	7.26 7.24	14.42 14.35)
15b	CH_3	2	86	143—145 (Ether)	1655	$C_{18}H_{21}N_3$	77.94 (78.20	6.90 6.97	15.15 14.96)
15b	CH_3	3	86	109—110 (IPE)	1605	$C_{19}H_{21}N_3$	78.32 (78.18	7.26 7.25	14.42 14.25)

a) Melting point, IR spectra, and analytical data are described in Table III.

2-Oxo-3,3-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (22a)——To a solution of 0.26 g (5 mmol) of NaH (50% oil suspension) in 10 ml of DMF was added 1.56 g (5 mmol) of **21a**. The mixture was stirred at room temperature for 2 hr and poured into water. An insoluble solid was collected and recrystallized from $CHCl_3$–MeOH to give 1.20 g (87%) of **22a**, mp 280°. IR ν_{max}^{KBr} cm^{-1}: 1725, 1615. *Anal.* Calcd. for $C_{17}H_{15}N_3O$: C, 73.62; H, 5.45; N, 15.15. Found: C, 73.45; H, 5.54; N, 15.18.

2-Oxo-3,3-diphenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]pyrimidine (22b)——Compound **21b** (1.64 g 5 mmol) was treated with 0.26 g of NaH (50% oil suspension) as described in the synthesis of **22a** to give 1.28 g (88%) of **22b**, mp 280° (from $CHCl_3$–MeOH). IR ν_{max}^{KBr} cm^{-1}: 1710, 1630. *Anal.* Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.07; H, 5.92; N, 15.58.

Reduction of Oxobicyclic Guanidines (17, 18, 22 and 28) with Sodium Bis(2-methoxyethoxy)aluminum Hydride (Red-Al) General Method——To a suspension of 1.00 g of oxo-bicyclic guanidine in 30 ml of THF was added Red-Al at 0°. The mixture was heated under refluxing for times as shown in Table III. After cooling, to the mixture was added an aqueous Na_2SO_4 solution and large amounts of water. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from AcOEt or benzene to give the product. These reation results are shown in Table III, along with the reaction conditions.

Reaction of 1-(ω-Chloroalkyl)-2-ethoxy-4,4-diphenyl-2-imidazolines (14) with Amines General Method——A mixture of 3.0 g of **14** with 50 ml of 10% NH_3–MeOH solution in a sealed tube or 50 ml of 20% $MeNH_2$ aqueous EtOH was heated at 80—120° for 5—10 hr. After cooling, the mixture was concentrated *in vacuo*. The residue was mixed with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from the solvent such as ether, isopropylether (IPE) or acetone to give **4** and **15**. These reaction products are shown in Table IV.

Cyclization Reaction of 2-(ω-Hydroxyalkylimino)-4,4-diphenylimidazolidines (3)——To a solution of $SOCl_2$ was added 2.24 g (8 mmol) of **3a** at 0—5°. The mixture was allowed to stand at room temperature for 2 hr and concentrated *in vacuo*. To the residue was added a solution of 4.0 g of KOH in 40 ml of 50% aqueous MeOH and the mixture was refluxed for 2 hr. The mixture was concentrated to remove MeOH *in vacuo*. The residual mixture was extracted with ether. The extract was evaporated *in vacuo* to give 1.8 g of oily mixture of **4a** and **5a**. The mixture was treated with small amount of AcOEt to give crystal of **5a**, yield 0.61 g (29%). The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (30 g). After elution with $CHCl_3$, the fraction with MeOH–$CHCl_3$ was collected to give 0.06 g (3%) of **4a**.

Following the same method, cyclization reaction of 3.55 g (12 mmol) of **3b** gave crystalline mixture of **4b** and **5b** in 90% yield. The mixture was separated by fractional recrystallization from AcOEt to give 0.75 g (22%) of **4b** and 0.60 g (18%) of **5b**.

8-Methyl-2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (15b)——A mixture of 0.83 g (3 mmol) of **4b** and 0.12 g of NaH (50% oil suspension) in 30 ml of DMF was stirred at room temperature for 1 hr. To the mixture was added 0.45 g (3.2 mmol) of MeI. The mixture was stirred for 3 hr and poured into water. The mixture extracted with ether and the extract was evaporated *in vacuo*. The residue was recrystallized from ether–petr. ether to give 0.44 g (50%) of **15b** which was identical with a sample prepared from **14b** and $MeNH_2$.

8-Acetyl-2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (25)——To a solution of 2.00 g (7.2 mmol) of **4b** and 0.80 g (7.9 mmol) of Et_3N in 30 ml of $CHCl_3$ was added 0.62 g (7.9 mmol) of AcCl with stirring at 0—5°. The solution was further stirred for 3 hr at the same temperature. The reaction mixture was washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo*. The residue was recrystallized from ether–petr. ether to yield 1.60 g (70%) of **25**, mp 75—76°. IR ν_{max}^{KBr} cm^{-1}: 1670, 1610. NMR ($CDCl_3$) δ: 3.91 (2H, s, C_3–CH_2), 3.76 (2H, t, C_7–CH_2), 3.13 (2H, t, C_5–CH_2), 2.68 (3H, s, CH_3), 1.90 (2H, m, C_6–CH_2). *Anal.* Calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.61; H, 6.65; N, 13.12.

8-Benzoyl-2,2-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (26)——Following the procedure for the synthesis of **25**, compound **4b** (2.00 g, 7.2 mmol) was treated with 1.11 g (7.9 mmol) BzCl and 0.90 g (7.9 mmol) of Et_3N in 30 ml of $CHCl_3$ to give 2.30 g (82%) of **26**, mp 190—191° (from AcOEt–ether). IR ν_{max}^{KBr} cm^{-1}: 1660, 1620. NMR ($CDCl_3$) δ: 3.83 (2H, s, C_3–CH_2), 3.80 (2H, t, C_7–CH_2), 3.19 (2H, t, C_5–CH_2), 2.06 (2H, m, C_6–CH_2). *Anal.* Calcd. for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.01. Found: C, 79.02; H, 6.10; N, 11.08.

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