[Chem. Pharm. Bull. 17(12)2436—2441(1969)]

UDC 547.783.07.04

Studies on Syntheses of Thiohydantoin Related Compounds. XVII.[1] Synthesis of 1,3-Diphenyl-5-butylhydantoin

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(Received February 17, 1969)

1,3-Diphenyl-5-butylhydantoin(I) was synthesized by two methods, indirect and direct, with the object of the development of a new analgesic agent. In the course of the indirect method, treatment of 1,3-diphenyl-2-thiohydantoin(IV) with *n*-butylaldehyde gave 1,3-diphenyl-5-butylidene-2-thiohydantoin(V) as two kinds of crystals, which were confirmed to be geometrical isomers with each other. The configurations of them were determined from the NMR spectral data. Two by-products obtained in this reaction was also geometrical isomers with each other, and they were deduced to be dimers of 1,3-diphenyl-5-butylidene-2-thiohydantoin, 1,3-diphenyl-5-{β-ethyl-γ-(1,3-diphenyl-2-thiohydantoinyl)} hexylidene-2-thiohydantoin (Xa and Xb) from some physical data. In the direct method, 1,3-diphenyl-5-butylhydantoin was obtained in 40% yield by refluxing 2-anilinohexanoic acid (IX) and phenyl isocyanate in xylene.

Some investigations[3] on hydantoin derivatives possessing an analgesic activity have been made, but any utilizable ones have not yet been synthesized. Interest in the development of the more effective analgesic agent has led to the suggestion that 1,3-diphenyl-5-butylhydantoin (I), a structural isomer of phenylbutazone (II) used as an analgesic and antiinflammatory agent so frequently, might also have analgesic action.

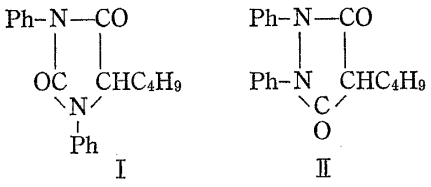

Chart 1

1,3-Diphenyl-5-butylhydantoin was obtained by two methods. One is an indirect method introducing butyl group into 1,3-diphenyl-2-thiohydantoin (IV), and the other is a direct method condensing 2-anilinohexanoic acid (IX) with phenyl isocyanate.

In the indirect method the authors could obtain geometrical isomers of 1,3-diphenyl-5-butylidene-2-thiohydantoin (V) as intermediate products and determine the configurations of them. Although many investigations on geometrical isomers of hydantoin compounds have hitherto been made, they dealt almost exclusively with 5-arylidenehydantoins, *i.e.* 1,3-diphenyl-5-benzylidene-2-thiohydantoin,[4] 1,3-dimethyl-5-anisalhydantoin,[5] and 5-(α-chloro-*o*-nitrobenzylidene)hydantoin,[6] and so on. The geometrical isomers of 5-alkylidenehydantoins have not yet been reported with the exception of the isomers of 1-phenyl-5-carboxymethylenehydantoin.[7] In that case, however, the *trans* and *cis* isomers were obtained by their respective reactions not by one reaction, and only the ultraviolet spectral data were presented as a proof of the configurations of the isomers.

1) Part XVI: H. Shirai and T. Yashiro, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **15**, 47 (1967).
2) Location: *3-1, Tanabe-dori, Mizuho-ku, Nagoya.*
3) E.A. Swinyard, D.L. Smith, and L.S. Goodman, *J. Am. Pharm. Assoc.*, **43**, 212 (1954); Distillers Co., Ltd., Fr. Patent M2597 (1964) [*Chem. Abstr.*, **62**, 1667 (1965)]; Sankyo Co., Ltd., Japan Patent 23405 (1964) [*Chem. Abstr.*, **62**, 11820 (1965)]; J.J. Shroff and J.J. Trivedi, *J. Indian Chem. Soc.*, 43, 787 (1966).
4) T.B. Johnson and S.E. Hadley, *J. Am. Chem. Soc.*, **37**, 171 (1915).
5) M.K. Seikel, *J. Am. Chem. Soc.*, **59**, 436 (1937).
6) H.R. Henze and G.R. Allen, Jr., *J. Am. Chem. Soc.*, **77**, 461 (1955).
7) R.K. Ralph, G. Shaw, and R.N. Naylor, *J. Chem. Soc.*, **1959**, 1169.

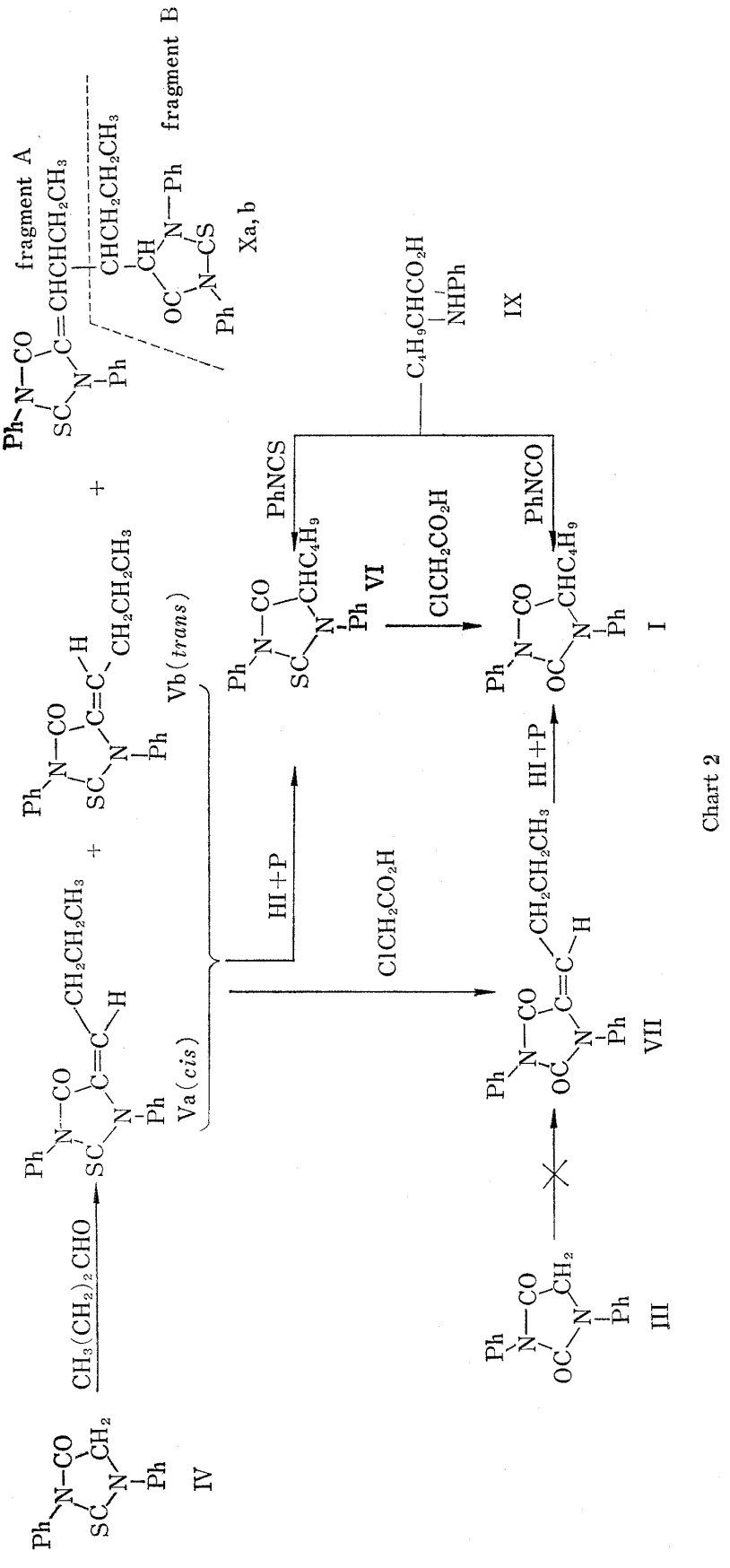

Chart 2

In this paper, in connection with the synthesis of I, separation of the geometrical isomers obtained by the condensation of IV and *n*-butylaldehyde and determination of their configurations are described as part of the studies on syntheses of thiohydantoin related compounds.

Since 1,3-diphenylhydantoin (III) did not react with *n*-butylaldehyde by any means, 1,3-diphenyl-2-thiohydantoin[8] (IV) which has larger reactivity was taken as a starting material. Condensation of IV and *n*-butylaldehyde in pyridine containing triethylamine followed by fractionating the reaction mixture with column chromatography on silica gel furnished four crystalline products as shown in Table I.

Table I. Physical and Analytical Data of Compound V and X

Compd. No.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR $\nu_{max}^{CHCl_3}$ cm^{-1} -C=O	-C=C-	-C=S
Va	85— 86	32.5	$C_{19}H_{18}ON_2S$	70.81	5.59	8.67	71.14	5.88	8.39	1747	1651	1342
Vb	126—128	20.6	$C_{19}H_{18}ON_2S$	70.81	5.59	8.67	70.69	5.85	9.02	1750	1663	1337
Xa	232—234	2.2	$C_{38}H_{36}O_2N_4S_2$	70.81	5.59	8.67	70.83	5.66	8.90	1750	1646	1336
Xb	264—266	5.8	$C_{38}H_{36}O_2N_4S_2$	70.81	5.59	8.67	70.34	5.55	8.87	1758	1664	1333

Since their infrared (IR) spectra all contained bands at 1646 cm^{-1} to 1664 cm^{-1}, assignable to the C=C stretching vibration, and some characteristic absorption bands of 2-thiohydantoin ring, and furthermore their analytical data showed that they have a good agreement with the elemental composition ($C_{19}H_{18}ON_2S$) of 1,3-diphenyl-5-butylidene-2-thiohydantoin (V), they were all reasonably thought to be V. However, the molecular weights of Va and Vb were estimated to be 310 and 322, while those of Xa and Xb were about twice as much; 611 and 658 respectively. The ultraviolet spectra of Va and Vb, those of Xa and Xb as well, closely resembled each other respectively. When they were reduced with 57% hydroiodic acid and red phosphorus, Va and Vb gave the same product, 1,3-diphenyl-5-butyl-2-thiohydantoin (VI), which was identical with the specimen obtained by the direct method as described later, and Xa and Xb gave also the same product with the melting point of 264—266° and the elemental composition of $C_{38}H_{38}O_2N_4S_2$.

In view of the above facts, it seemed reasonable to assume that Va and Vb are geometrical isomers of V, and Xa and Xb are those of a dimer of V, each other. The fact that Vb and Xb were obtained respectively by isomerization of Va and Xa in 95% ethanol saturated with hydrogen chloride lended a further confirmation of being geometrical isomer. The configurations of Va and Vb were assigned respectively to be *cis* and *trans* on the basis of the following nuclear magnetic resonance (NMR) spectral data.

Thus, the NMR spectrum of Va displayed a vinyl proton at 5.39 ppm (triplet) and two methylene groups of 2.68 (quartet) and 1.42 ppm (sextet). On the other hand, the spectrum of Vb displayed a vinyl proton at lower field, 6.03 ppm, than Va because of the effect of bond anisotropy of the carbonyl group adjacent to the ethylene bond, and two methylene groups (multiplet) at higher field, about 1.40 ppm, than Va as they would not be affected with bond anisotropy.

The most probable structure of Xa and Xb is supposed from some physical data to be X. The ultraviolet (UV) spectra of Xa and Xb showed the maxima at nearly 280 mμ due to the structure of VI and at nearly 330 mμ due to the structure of V. Although the mass spectra of Xa and Xb did not show a molecular ion peak, they gave fragments at *m/e* 321 (fragment A), 322 (fragment A+1), 323 (fragment B), and 324 (fragemnt B+1) attributable

8) H. Shirai, T. Yashiro, and I. Miwa, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **14**, 63 (1966).

to most likely cleavage of the molecular ion species. Furthermore, the NMR spectrum of Xa revealed the presence of a vinly proton (5.37 ppm, doublet), a proton of hydantoin ring (4.86 ppm, doublet), 20 aromatic protons due to 4 phenyl groups, and 14 alkyl protons.

The configurations of them are not yet determined owing to the unfavorable solubility of Xb in any solvent for measuring the NMR spectra.

Both Va and Vb were reduced to 1,3-diphenyl-5-butyl-2-thiohydantoin (VI) as described previously. Desulfurization of VI by heating in 50% aqueous monochloroacetic acid solution for 2 hours gave the aimed 1,3-diphenyl-5-butylhydantoin (I, bp 210—215°/3 mmHg) in 67% yield. I was also obtained in 31% overall yield when V was first desulfurized to 1,3-diphenyl-5-butylidenehydantoin (VII, mp 205—207°) by treatment with 65% aqueous monochloroacetic acid solution and then VII was reduced with 57% hydroiodic acid and red phosphorus.

Since the NMR spectrum of VII obtained from Va (*cis*) showed a vinyl proton as triplet at a closely similar position to the vinyl proton signal (5.39 ppm) of Va, 5.55 ppm, and two protons of the methylene group adjacent to the ethylene double bond as quartet at 2.77 ppm far from the signal of another methylene protons (multiplet at about 1.50 ppm), the configuration of VII was determined to be a *cis* form. The desulfurization of Vb afforded the same substance VII as from Va as a major product accompanied by a small amount of an unknown product which was supposed to be a geometrical isomer (*trans* form) of VII on account of the striking resemblance between its UV and IR spectra and those of VII, and a slight difference with VII in TLC on silica gel with chloroform. However, we could not investigate further about the unknown product, because only a very small amount of it was obtained.

Treatment of 2-bromohexanoic acid prepared from hexanoic acid and bromine by the method given in the literature[9] with aniline in benzene gave 2-anilinohexanoic acid (IX) in 88% yield. 1,3-Diphenyl-5-butylhydantoin (I) was obtained directly in 40% yield when IX was refluxed with phenyl isocyanate in xylene for 5 hours. 1,3-Diphenyl-5-butyl-2-thiohydantoin (VI) was obtained from IX and phenyl isothiocyanate in the same manner in 56% yield. The IR and NMR spectra of I and VI thus obtained agreed entirely with the specimens prepared by the indirect method respectively.

Although the analgesic activity of I and VI was examined by using mice, they did not exhibit any activity.

Experimental[10]

1,3-Diphenyl-5-butylidene-2-thiohydantoin (Va and Vb)——A solution of 3.0 g of 1,3-diphenyl-2-thiohydantoin and 1.5 ml of *n*-butyraldehyde in 10 ml of pyridine containing 3.0 ml of triethylamine was refluxed for 3 hr. After concentration of the solution under reduced pressure, the residue was dissolved in $CHCl_3$ and washed with 10% HCl, saturated $NaHCO_3$ aq. solution and water and dried over anhydrous Na_2SO_4. Removal of the solvent gave 3.1 g of a yellowish-brown syrup, which was chromatographed on 70 g of silica gel using $CHCl_3$ as solvent. A yellow syrup eluated first was crystallized by treatment with ether. The crude eluate was recrystallized from ether–petr. ether to give 1.17 g of Va as pale yellow prisms, mp 85—86°. NMR: 5.39 (1H, triplet, J=7.8, =CH–), 2.68 (2H, quartet, J=7.8, =CH–C<u>H</u>$_2$–), 1.42 (2H, sextet, J=7.8, 7.8, –C<u>H</u>$_2$–CH_3). Next eluate was recrystallized from ether–petr. ether to give 0.74 g of Vb as pale yellow plates, mp 126—128°. NMR: 6.03 (1H, triplet, J=8.0, =CH–), 0.98—1.70 (4H, multiplet, –CH_2–CH_2–).

Continued elution with $CHCl_3$ containing 0.5% EtOH gave 0.38 g of pale yellow solid separable to two crystalline products, 1,3-diphenyl-5-{β-ethyl-γ-(1,3-diphenyl-2-thiohydantoinyl)} hexylidene-2-thiohydantoin (Xa and Xb), by fractional crystallization using ether. Recrystallizations of them from $CHCl_3$–benzene afforded 0.08 g of yellow prisms (Xa) melting at 232—234° and 0.21 g of pale yellow needles (Xb) melting

9) H.T. Clarke and E.R. Taylor, "Organic Syntheses," Coll. Vol. I, ed. H. Gilman, John Wiley and Sons, Inc., New York, N.Y., 1956, p. 115.

10) All melting points were measured on a Yanagimoto micro-melting point determination apparatus and uncorrected. NMR spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ solution containing tetramethylsilane as an internal standard. Chemical shifts are expressed in ppm and coupling constants (J) in cps. Mass spectra were determined on a Hitachi RMU-6 spectrometer.

at 264—266° respectively. NMR of Xa: 7.25—7.80 (20H, multiplet, 4-C_6H_5), 5.37 (1H, doublet, $J=11.0$, =CH–), 4.86 (1H, doublet, $J=4.0$, –CO–CH<), 3.83–4.40 (1H, multiplet, =CH–CH<).

Isomerization of Xa to Xb——A solution of 0.1 g of Xa in 30 ml of 95% EtOH saturated with HCl gas was refluxed for 13 hr with letting in HCl gas occasionally. On cooling, 0.08 g (80%) of Xb was obtained as pale yellow needles melting at 264—266°. A greater part of the residue obtained by evaporation of the mother liquor was recognized as Xa in TLC on silica gel with $CHCl_3$.

Reduction of Xa and Xb——A mixture of 0.12 g of Xa or Xb, 0.3 ml of 57% HI, 0.02 g of red phosphorus, and 2.5 ml of AcOH was refluxed for 3 hr. After filtrating off red phosphorus, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$, washed with 5% $NaHSO_3$ aq. solution and water, and dried over anhydrous Na_2SO_4. The pale yellow syrup obtained by removal of the solvent was treated with ether to give colorless crystals. Recrystallization from $CHCl_3$–benzene gave 0.07 g (58%) of 1,3-diphenyl-5-{β-ethyl-γ-(1,3-diphenyl-2-thiohydantoinyl)} hexyl-2-thiohydantoin[11] as colorless sands, mp 264—266°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762 (C=O), 1323 (C=S). UV λ_{max}^{EtOH} mμ (log ε): 242 (4.17), 280.5 (4.09). *Anal.* Calcd. for $C_{38}H_{38}O_2N_4S_2$: C, 70.33; H, 6.21; N, 8.64. Found: C, 70.84; H, 5.90; N, 8.58.

1,3-Diphenyl-5-butyl-2-thiohydantoin (VI)——i) From Va or Vb: A mixture of 0.31 g of Va or Vb, 0.6 ml of 57% HI, 0.05 g of red phosphorus, and 5 ml of AcOH was refluxed for 1 hr. After filtrating off red phosphorus, the filtrate was treated by the same procedure described above. Recrystallization of crude crystals from ether–petr. benzin gave 0.21 g (67%) of VI as colorless needles, mp 120—122°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762 (C=O), 1323 (C=S). UV λ_{max}^{EtOH} mμ (log ε): 241 (4.20), 279.5 (4.08). NMR: 4.65 (1H, triplet, $J=4.1$, >CH–), 1.60—2.10 (2H, multiplet, >CH–C<u>H</u>$_2$–). *Anal.* Calcd. for $C_{19}H_{20}ON_2S$: C, 70.81; H, 5.59; N, 8.67. Found: C, 70.43; H, 5.88; N, 8.79.

ii) From IX: A solution of 17.2 g of 2-bromohexanoic acid and 17.2 g of aniline in 20 ml of benzene was refluxed for 2 hr. The crude product obtained by cooling was washed with benzene and water and recrystallized from 55% EtOH to give 15.2 g (88%) of IX as colorless plates, mp 151—152°. IR ν_{max}^{KBr} cm^{-1}: 2200—2700 (NH_2^+), 1550—1600 (NH_2^+, COO^-). *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.57; H, 8.21; N, 6.76. Found: C, 69.48; H, 8.25; N, 6.85. A mixture of 0.8 g of IX, 0.55 g of phenyl isothiocyanate, and 4 ml of xylene was refluxed for 5 hr and evaporated to dryness under reduced pressure. The crude product obtained by treating the residue with ether–petr. ether was washed with 5% aq. NaOH solution and water and recrystallized from ether–petr. benzin to give 0.7 g (56%) of VI, mp 120—122°.

1,3-Diphenyl-5-butylidenehydantoin (VII)——i) From Va: A mixture of 0.4 g of Va, 3.0 g of monochloroacetic acid, and 1.5 ml of water was refluxed for 3 hr. After cooling, water and then $CHCl_3$ were added to the reaction mixture and the $CHCl_3$ layer was washed with 2% NaOH aq. solution and water, and dried over anhydrous Na_2SO_4. The solvent was evaporated to afford 0.35 g of a pale yellow syrup, and the syrup was chromatographed on 5 g of alumina using benzene as solvent. Further chromatography of the syrupy eluate on 5 g of acidic alumina with ether gave crystals, which were recrystallized from ether–petr. ether to yield 0.22 g (57.9%) of VII as colorless prisms, mp 205—207°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727, 1776 (C=O), 1665 (C=C). UV λ_{max}^{EtOH} mμ (log ε): 221 (4.40). NMR: 5.55 (1H, triplet, $J=7.9$, =CH–), 2.77 (2H, quartet, $J=7.9$, 7.9, =CH–C<u>H</u>$_2$–), 1.14—1.80 (2H, multiplet, –C<u>H</u>$_2$–CH_3). *Anal.* Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.91; N, 9.15. Found: C, 74.50; H, 5.56; N, 9.42.

ii) From Vb: By the same procedure described for i), 0.16 g of a pale yellow syrup was obtained from 0.2 g of Vb, and the syrup was chromatographed on 8 g of silica gel using $CHCl_3$ as solvent. The same chromatography on acidic alumina of the first eluate and recrystallization as described above for i) gave 0.08 g (42.1%) of VII as colorless prisms, mp 205—207°. For physical constants see i). Further chromatography of the second eluate on 3 g of acidic alumina with ether afforded 0.01 g of an unknown product as a colorless syrup which was presumed to be a *trans* isomer of VII. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732, 1778 (C=O), 1671 (C=C). UV λ_{max}^{EtOH} mμ (log ε): 220.5 (4.35).

1,3-Diphenyl-5-butylhydantoin (I)——i) From VI: A mixture of 0.5 g of VI, 4.5 g of monochloroacetic acid, and 4.5 ml of water was refluxed for 3 hr. After cooling, 50 ml of water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The extract was washed with 2% NaOH aq. solution and water and dried over anhydrous Na_2SO_4. The syrupy residue obtained by removal of the solvent was chromatographed on 25 g of acidic alumina using ether as solvent and 0.32 g (67.4%) of I was obtained as a colorless syrup, bp 210—215° (3 mmHg) (bath temp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718, 1779 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 239 (4.26). NMR: 4.73 (1H, triplet, $J=4.1$, >CH–), 1.70—2.20 (2H, multiplet, >CH–C<u>H</u>$_2$–), 1.03—1.50 (4H, multiplet, –C<u>H</u>$_2$–C<u>H</u>$_2$–CH_3). *Anal.* Calcd. for $C_{19}H_{20}O_2N_2$: C, 73.96; H, 6.55; N, 9.10. Found: C, 74.12; H, 6.74; N, 8.89.

ii) From VII: By the same procedure described for reduction of Xa and Xb, 0.11 g of a pale yellow syrup was obtained from 0.15 g of VII after removal of the solvent. Chromatography of the syrup on 5 g of acidic alumina with ether gave 0.08 g (53.2%) of I as a colorless syrup, bp 210—215° (3 mmHg) (bath temp.). For physical constants see i).

11) The authors could not determine the NMR spectrum of this compound since it did not dissolve in any solvent for measuring NMR spectra.

iii) From IX: A mixture of 2.0 g of IX, 1.1 g of phenyl isocyanate, and 15 ml of xylene was refluxed for 5 hr. The crystals formed by cooling was filtered off, washed with 5% NaOH aq. solution and water, and recrystallized from EtOH to yield 0.07 g of 1,3-diphenylurea as colorless needles, mp 247—248.5°. The filtrate was concentrated under reduced pressure. The ether solution of the residue was washed with 5% NaOH aq. solution and water and dried over anhydrous Na_2SO_4. A viscous syrup resulted by removal of the solvent was chromatographed on 50 g of acidic alumina using ether as solvent, to give 1.2 g (40.3%) of I as a colorless syrup, bp 210—215° (3 mmHg) (bath temp.).

Acknowledgement We are grateful to Miss T. Yamagishi of this Faculty for microanalyses, and to Mr. Y. Deguchi and N. Nakanishi (late) of the Central Analysis Room, Faculty of Pharmaceutical Sciences, Meijo University for NMR and Mass spectral measurements.