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Prodrug-Oriented Molecular Design of Neonicotinoids: Preparation of Imidacloprid-Related 5,5-Dimethoxy-1,3-diazacyclohexane Derivatives and Their Insecticidal Activity

Shinzo KAGABU,[1,†] Manabu HIBI,[1] and Keiichiro NISHIMURA[2]

[1]*Department of Chemistry, Faculty of Education, Gifu University, Gifu 501-1193, Japan*
[2]*Research Institute for Advanced Science and Technology, Osaka Prefecture University, Osaka 599-8570, Japan*

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Prodrug-oriented molecular design was attempted for the potent acyclic neonicotinoid insecticide, clothianidin (1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine). Molecules bearing a CH_2COCH_2 bridge linking the 1,3-NH ends of clothianidin or their acetals would possibly be hydrolyzed, regenerating the mother compounds. This strategy was used to prepare seven acetals of clothianidin-based molecules that combined 2-chloro-5-thiazolylmethyl, 6-chloro-3-pyridylmethyl or 3-tetrahydrofurfuryl with a nitroimine, cyanoimine or nitromethylene group. The key intermediate, 1,3-diamino-2,2-dimethoxypropane, was prepared from the dihydroxyacetone dimer in four steps. A selected acetal showed a characteristic nerve-impulse pattern for neonicotinoids on an excised American cockroach ganglion, although the neuroblocking activity was fairly low. Some acetals were highly insecticidal against the pea aphid at 0.8–20 ppm 7 days after a spray treatment, this being in a contrast to their far weaker activity by injection into American cockroaches. The biological results suggest that the intrinsic insecticidal activities of the acetals are weak, but would exhibit enhanced activity if hydrolyzed in an external environment.

Key words: neonicotinoid insecticide; prodrug; clothianidin; acetal; neuroblocking activity

The molecular design of a so-called prodrug, a transformation of an original active molecule in order to show or to enhance its biological activity, is found time and again in developed pesticides.[1)] Prodrug-based design can also be seen in the neonicotinoid field.[2)]

The potent insecticide, clothianidin (**1**),[3)] may be an accessible target for prodrug molecular design because of its structure bearing two reactive amine ends. If one can make up the structure of clothianidin by linking the amine ends so as to undo the linker before reaching the site of action, the modified molecule would exhibit potency due to clothianidin. The construction of triazine and thiadiazine (**6**, Y = NMe or S) are examples of this strategy. In fact, clothianidin can be readily regenerated from these molecules under hydrolytic conditions (Fig. 1, eq. 1).[2)] The oxadiazine derivative, thiamethoxam (**5**), can be viewed as a structure by the same type of modification and, in principle, this skeleton can be hydrolyzed, leaving clothianidin.[4)] Nevertheless, in spite of the formally similar appearance, thiamethoxam seems to have some different biological features from those of the triazine and thiadiazine analogues.[5)] We have attributed its distinctive biological performance to the relatively strong $–NCH_2–O–CH_2N–$ linkage by comparing the bond energy of C–O with that of C–N or C–S.[6)] Thiamethoxam proved practically unchanged under hydrolytic conditions.[7)]

These examples indicate that some molecules designed by a prodrug approach can display discrete biological features that are different not only from the original molecule, but also from similar structural variants. We attempted in this study to contrive another reconstruction of clothianidin. The basic skeleton of neonicotinoid is constructed from an amidine or a guanidine conjugated to a powerful electron-withdrawing group like a nitro or cyano one; consequently, the amidinyl (guanidyl) nitrogen atoms are partially positive.[8–10)] By referring to the well-examined hydrolytic cleavage of 1,3-diacyl and related structures[11,12)] as represented by the reaction, $RCOCH_2COR + H_2O \rightarrow RCOOH + RCOCH_3$, we predicted that such a β-aminoketone as $R_1R_2NCH_2COCH_3$ could give $R_1R_2NCH_3$ in a similar fashion, if the amine part were positively charged like the nitrogen atoms in the neonicotinoid skeleton. Thus, 1,3-diazacyclohexa-5-one derivatives (**8**) would eventually decay to clothianidin-type acyclic molecules in the applied environment as illustrated in Fig. 1 (eq. 2). Also, we expected another biological profile to be shown due to the different bonding properties from the existing modifications. Acetal is a well-known protective group of ketone and is, in principle, deprotected under hydrolytic conditions.[13)] With this strategy in mind, we prepared a set of

† To whom correspondence should be addressed. Fax: +81-58-293-2207; E-mail: kagabus@cc.gifu-u.ac.jp

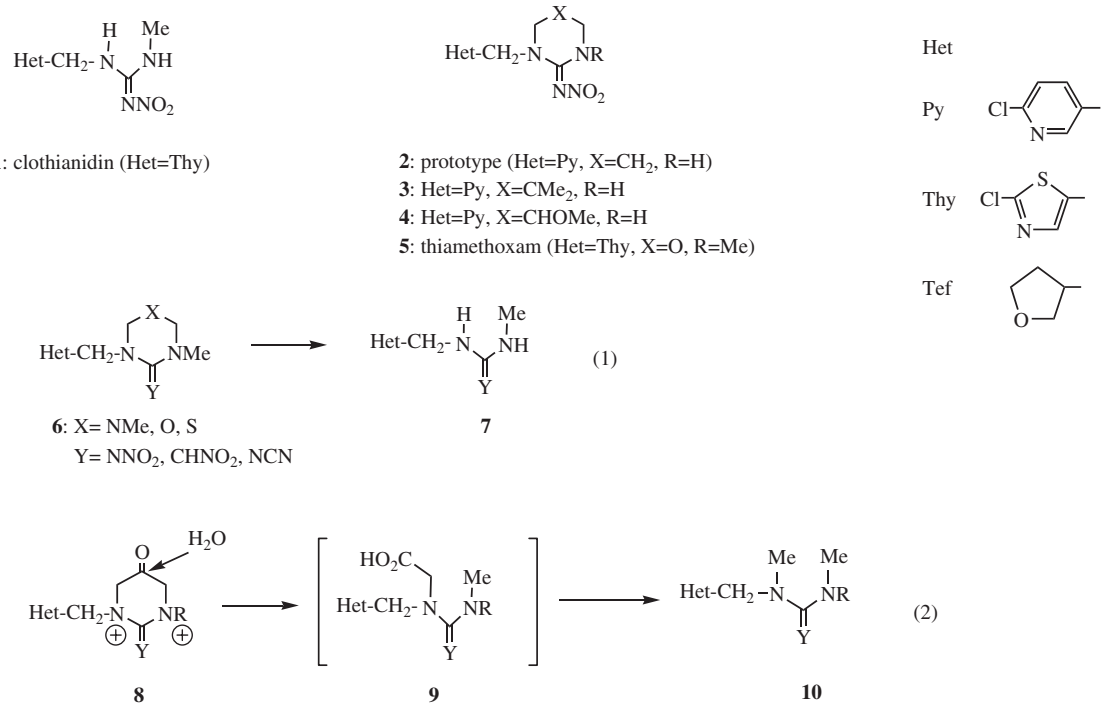


Fig. 1. Hydrolysis Paths (eqs. 1 and 2) for Clothianidin and Thiamethoxam and Related Compound. The table on the right shows the abbreviations of the heterocyclic structural elements.

diazacyclohexanone acetals bearing various functional groups and examined their biological activity toward insects.

Materials and Methods

Preparation of the compounds.

All melting point (mp) data are uncorrected. IR spectra were measured with a Perkin Elmer FTIR 1600 spectrometer, and NMR spectra were obtained by a Varian Gemini 2000 C/H (400 MHz) instrument. The chemical shifts were recorded in δ (ppm) and the coupling constants, J, in Hz. Mass spectra were recorded by a Jeol JMS-700 instrument (EI, 70 eV).

*2,2-Dimethoxypropanediol (**12**).* To a solution of dihydroxyacetone dimer (15.0 g, 0.05 mmol) in dried methanol (200 ml) was added trimethyl orthoformate (17.5 g, 0.16 mol) and *p*-toluenesulfonic acid (0.06 g). The mixture was stirred for 24 h at ambient temperature, before anhydrous sodium carbonate (180 mg) was added and stirring continued for a further 24 h. Most of the methanol was evaporated, and the residue was chromatographed on silica gel with chloroform as the eluent, giving 7.60 g (50% yield) of a product as a colorless liquid. The spectral data were identified by the reported data for **12**.[14)]

*2,2-Dimethoxy-1,3-propanediol bismethanesulfonate (**13**).* A solution of methanesulfonyl chloride (12.8 g, 0.28 mol) in pyridine (150 ml) was added dropwise to 2,2-dimethoxypropanediol (13.6 g, 0.1 mol) while ice cooling. After 4 hour of stirring, the reaction mixture was poured into a solution composed of 15 ml of water and 30 ml of conc. HCl with *ca.* 50 g of crushed ice, the solution being acidified to pH 3 by further adding a 10% HCl solution. This mixture was extracted with chloroform (4×30 ml), the chloroform layer being washed with a 10% HCl solution (2×10 ml), and then with water and finally dried over magnesium sulfate. Evaporation of the solvent and subsequent recrystallization of the residual solid from ether gave 19.7 g (67.1%) of the product as colorless crystals, mp 102–103 °C. IR ν_{max} (KBr): 1350, 1330, 1180 cm^{-1}. NMR δ_H ($CDCl_3$): 3.10 (6H, s), 3.33 (6H, s), 4.23 (4H, s); δ_C: 37.7, 48.8, 63.6, 98.0. MS m/z (%): 292 (M^+, 5), 261 (70), 166 (100), 103 (20). *Anal.* Found: C, 28.29; H, 5.50; S, 21.60%. Calcd. for $C_7H_{16}O_8S_2$: C, 28.26; H, 5.52; S, 21.93%.

*1,3-Diamino-2,2-dimethoxy-1,3-propanediol bis-p-toluenesulfonate (**14**).* This compound was prepared according to the above-mentioned procedure, but using *p*-toluenesulfonyl chloride instead of methanesulfonyl chloride. Yield: 76.5%. Mp 113–115 °C. IR ν_{max} (KBr): 1350, 1190, 1175 cm^{-1}. NMR δ_H ($CDCl_3$): 2.46 (6H, s), 3.10 (6H, s), 3.92 (4H, s), 7.35 (2H, d, $J = 8.2$), 7.75 (2H, d, $J = 8.2$); δ_C: 21.7, 48.3, 63.8, 97.9, 128.0, 130.0, 132.1, 145.3. MS m/z (%): 259 (M^+, 100), 103 (18). *Anal.* Found: C, 51.50; H, 5.60; S, 14.90%. Calcd. for $C_{19}H_{24}O_8S_2$: C, 51.34; H, 5.44; S, 14.43%.

*1,3-Diazido-2,2-dimethoxypropane (**15**).* Sodium azide (6.86 g, 112 mmol) was added to a solution of bismethanesulfonate (**13**; 7.69 g, 26.3 mmol) in hexamethylphosphoramide (120 ml). The mixture was stirred for 60 h at 120 °C, before being cooled to room

temperature, diluted with 200 ml of water, and extracted with isopropyl ether (IPE; 3 × 30 ml). The combined IPE layers were dried over magnesium sulfate. After evaporating IPE at below 40 °C, chromatography of the residue on silica gel with a mixture of hexane and ethyl acetate (9:1, v/v) gave a colorless liquid. This product was used in the next step without further purification. Crude yield: 2.90 g (59.9%). IR (NaCl, neat): 2110, 1140 cm^{-1}. NMR δ_H ($CDCl_3$): 3.29 (6H, s), 3.42 (4H, s); δ_C: 48.8, 50.25, 100.8.

The yield of **15** was 10% by using tosylate **14** instead of mesylate **13** after 120 h of stirring at 120 °C in DMF.

*1,3-Diamino-2,2-dimethoxypropane (**16**).* A solution of diazide **15** (2.03 g, *ca.* 11.0 mmol) in 50 ml of methanol was hydrogenated with 135 mg of 10% palladium/carbon at atmospheric pressure. After 15 hour of shaking, the organic layer was filtered and the filtrate was distilled, quantitatively giving a diamine (1.47 g) with a boiling point of 100–104 °C at 20 mmHg. IR (NaCl, neat): 3280, 1600, 1460 cm^{-1}. NMR δ_H ($CDCl_3$): 1.40 (4H, bs), 2.85 (4H, s), 3.23 (6H, s); δ_C: 41.3, 48.1, 102.8. MS *m/z* (%): 122 (M^+, 2), 104 (100), 74 (88), 72 (98). HRMS (EI) M/z (M^+): calcd. for $C_4H_{14}N_2O_2$, 122.1055; found, 122.1056.

*2-Nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**17**).* To an ice-cooled solution of 1,3-diamino-2,2-dimethoxypropane (**16**) (0.33 g, 2.46 mmol) was added *S*,*S*′-dimethyldithionitroiminocarbonate (0.41 g, 2.46 mmol) in small portions. The mixture was stirred at room temperature for 3 h, the precipitated crystals were filtered and washed thoroughly with hexane. Yield: 280 mg (55.8%). Mp: 197 °C (dec). IR (KBr): 1620, 1610, 1380, 1300, 1100 cm^{-1}. NMR δ_H (DMSO-d_6): 3.20 (6H, s), 3.36 (4H, s), 8.85 (1H, bs); δ_C: 43.9, 48.6, 156.4. MS *m/z* (%): 205 (M^+, 32), 158 (33), 129 (100). *Anal.* Found: C, 35.29; H, 5.90; N, 27.60%. Calcd. for $C_6H_{12}N_4O_4$: C, 35.29; H, 5.93; N, 27.44%.

*2-(6-Chloro-3-pyridylmethyl)-5,5-dimethoxy-1,4,5,6-tetrahydro-[2H]-pyrimidine (**22**).* A solution of 1,3-diamino-2,2-dimethoxypropane (1.47 g, 11.1 mmol) and 6-chloronicotinaldehyde (1.25 g, 8.88 mmol) in 30 ml of benzene was refluxed for 3 h using a Dean-Stark trap. The residual liquid, after evaporating the benzene, was used in the next step without further purification. IR (NaCl, neat): 1455, 1105, 1049, 747, 734 cm^{-1}. NMR δ_H ($CDCl_3$): 2.32 (2H, d, $J = 13.7$), 2.87 (2H, d, $J = 13.7$), 3.25 (3H, s), 3.27 (3H, s), 4.63 (1H, s), 7.30 (1H, d, $J = 8.6$), 7.89 (1H, dd, $J = 8.6/2.3$), 8.62 (1H, d, $J = 2.3$); δ_C: 48.0, 49.4, 69.5, 92.8, 123.7, 135.6, 137.3, 148.5, 150.1. MS *m/z* (%): 256 (M^+, 0.7), 199 (6), 126 (28), 104 (85), 58 (100). HRMS (EI) M/z (M^+): calcd. for $C_{11}H_{16}ClN_3O_2$, 257.0932; found, 257.0941.

*2-(Tetrahydrofuran-3-ylmethyl)-2,2-dimethoxy-1,4,5,6-[2H]-tetrahy-dropyrimidine (**23**).* This compound was prepared according to the procedure used for **22** with 3-tetrahydrofurancarbaldehyde. IR (NaCl, neat): 1455, 1105, 1047, 897, 753 cm^{-1}. NMR δ_H ($CDCl_3$): 1.54 (2H, bs), 1.80 (1H, m), 2.02 (1H, m), 2.15 (1H, m), 2.30 (1H, m), 2.67 (2H, m), 3.21 (6H, s), 3.24 (2H, m), 3.65 (1H, 1H, m), 3.75 (1H, m), 3.89 (2H, m); δ_C: 29.7, 44.8, 47.9, 49.7, 49.8, 68.3, 71.0, 73.8, 93.1. MS *m/z* (%): 216 (M^+, 2), 186 (14), 145 (77), 88 (100). HRMS (EI) M/z (M^+): calcd. for $C_{10}H_{20}N_2O_3$, 216.1473; found, 216.1479.

*N-(6-Chloro-3-pyridylmethyl)-2,2-dimethoxy-1,3-diaminopropane (**24**).* A solution of compound **22** (~2.5 g) in a mixture of ethanol and water (5:1, v/v) was treated with 1.35 g of sodium borohydride in portions. The mixture was stirred for 120 h at room temperature. The inorganic solids were filtered off, and the resulting filtrate was concentrated. The residual semisolid was extracted with acetonitrile, and the acetonitrile was evaporated. This operation was repeated, and the combined residue was used for the next step without further purification. A small portion of the residue was distilled in a micro-distillation apparatus (100 °C, 0.1 mmHg) for analysis. IR (NaCl, neat): 1568, 1455, 1046 cm^{-1}. NMR δ_H ($CDCl_3$): 2.74 (2H, s), 2.86 (2H, s), 3.20 (6H, s), 3.80 (2H, s), 7.29 (1H, d, $J = 8.6$), 7.68 (1H, dd, $J = 8.6/2.3$), 8.33 (1H, d, $J = 2.3$); δ_C: 42.9, 48.2, 48.9, 50.5 102.1, 124.0, 134.6, 138.6, 149.3, 150.1. MS *m/z* (%): 259 (M^+, 1), 227 (38), 126 (13), 103 (23), 88 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{11}H_{18}ClN_3O_2$, 259.1089; found, 259.1091.

*N-(Tetrahydrofuran-3-ylmethyl)-2,2-dimethoxy-1,3-diaminopropane (**25**).* This compound was similarly prepared from **23**. IR (NaCl, neat): 1460, 1105, 1050 cm^{-1}. NMR δ_H ($CDCl_3$): 1.12 (1H, m), 1.59 (1H, m), 2.02 (1H, m), 2.37 (1H, m), 2.63 (2H, m), 2.77 (1H, m), 2.82 (2H, m), 3.22 (6H, s), 3.50 (1H, m), 3.82 (1H, m), 3.86 (2H, m); δ_C: 30.5, 39.6, 43.0, 48.1, 49.9, 53.5, 67.8, 71.9, 102.3. MS *m/z* (%): 220 ($M^+ + 2$, 44), 219 ($M^+ + 1$, 55), 186 (33), 158 (43), 104 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{10}H_{22}N_2O_3$, 218.1630; found, 218.1632.

*1-(6-Chloro-3-pyridylmethyl)-2-nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**18**).*

Method 1. A solution of diamine **24** (1.68 g, 6.49 mmol) and *S*,*S*′-dimethyldithionitroiminocarbonate (1.10 g, 6.62 mmol) in 10 ml of chloroform was stirred for 12 h at room temperature. The chloroform was distilled off and the residual liquid was subjected to preparative thin-layer chromatography on silica gel using a mixture of chloroform and ethanol (20:1, v/v) as the eluent, giving 140 mg (40% yield) of colorless crystals with mp 169 °C. IR ν_{max} (KBr): 3274, 1596, 1558, 1448, 1333, 1248, 1130, 1093 cm^{-1}. NMR δ_H ($CDCl_3$): 3.21 (6H, s), 3.35 (2H, m), 3.50 (2H, m), 4.71 (2H, s), 7.34 (1H, d, $J = 8.1$), 7.75 (1H, dd, $J = 8.1/2.6$), 8.31 (1H, d, $J = 2.6$), 9.87 (1H, bs); δ_C: 43.9, 48.9, 49.4, 50.7, 92.9, 124.7, 130.2, 139.0, 149.0, 151.4, 155.8. MS *m/z* (%): 330 (M^+, 2), 283 (79), 126 (54), 45 (100). *Anal.* Found: C, 43.59; H, 5.03; N, 21.60%. Calcd. for $C_{12}H_{16}ClN_5O_4$: C, 43.71; H, 4.89; N, 21.24%.

Method 2. To an ice-cooled solution of 2-nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**17**; 0.30 g, 1.47 mmol) in DMF was added sodium hydride (60%,

25 mg, 0.625 mmol) and the mixture was stirred for 30 min at room temperature. A solution of 6-chloro-3-pyridylmethyl chloride (240 mg, 1.47 mmol) in 4 ml of DMF was next added dropwise. The mixture was stirred overnight, before DMF was distilled off under reduced pressure. Preparative thin-layer chromatography on silica gel of the residue gave the product in a 43.5% yield (130 mg).

*1-(2-Chloro-5-thiazolylmethyl)-2-nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**19**).* This compound was prepared according to the foregoing method 2, using 2-chloro-5-thiazolylmethyl chloride instead of 6-chloro-3-pyridylmethyl chloride. Yield: 12%. Mp: 177 °C. IR ν_{max} (KBr): 3282, 1594, 1555, 1463, 1423, 1331, 1235, 1122, 1094, 1072, 1046 cm^{-1}. NMR δ_H ($CDCl_3$): 3.22 (6H, s), 3.42 (2H, m), 3.48 (2H, m), 4.70 (2H, s), 7.48 (1H, s), 9.72 (1H, bs); δ_C: 44.1, 46.0, 48.8, 50.6, 93.1, 134.6, 140.6, 154.2, 155.2. MS *m/z* (%): 336 (M^+, 3), 289 (51), 253 (100), 132 (85). *Anal.* Found: C, 35.64; H, 4.13; N, 21.00; S, 9.89%. Calcd. for $C_{10}H_{14}ClN_5O_4S$: C, 35.77; H, 4.20; N, 20.86; S, 9.55%.

*1-(6-Chloro-3-pyridylmethyl)-3-methyl-2-nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**20**).* To an ice-cooled solution of **18** (80 mg, 0.309 mmol) in 2.5 ml of DMF was added sodium hydride (60%, 25 mg, 0.625 mmol). After 30 min of stirring at room temperature, methyl iodide (140 mg, 1.00 mmol) in 2.5 ml of DMF was added dropwise. The mixture was stirred for 5 h at 60 °C, and subsequently DMF was distilled off under reduced pressure. Preparative thin-layer chromatography on silica gel of the residue gave the product in a 37.7% yield (40 mg). Mp: 136 °C. IR ν_{max} (KBr): 1605, 1397, 1278 cm^{-1}. NMR δ_H ($CDCl_3$): 3.17 (3H, s), 3.18 (6H, s), 3.33 (2H, m), 3.51 (2H, m), 4.70 (2H, s), 7.36 (1H, d, $J = 8.2$), 7.78 (1H, dd, $J = 8.2/2.5$), 8.31 (1H, d, $J = 2.5$); δ_C: 39.0, 49.1, 50.5, 51.7, 53.5, 94.0, 124.9, 129.3, 139.4, 149.2, 151.9, 158.2. MS *m/z* (%): 344 (M^+, 2), 297 (98), 169 (50), 126 (100). *Anal.* Found: C, 45.29; H, 5.30; N, 20.30%. Calcd. for $C_{12}H_{16}ClN_5O_4$: C, 45.42; H, 5.28; N, 20.37%.

*1-(2-Chloro-5-thiazolylmethyl)-3-methyl-2-nitroimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**21**).* This compound was similarly prepared from **19**. Yield: 23.5%. Mp: 157 °C. IR ν_{max} (KBr): 1598, 1528, 1415, 1383, 1333, 1296, 1090, 1048 cm^{-1}. NMR δ_H ($CDCl_3$): 3.13 (3H, s), 3.22 (6H, s), 3.40 (2H, m), 3.48 (2H, m), 4.75 (2H, s), 7.19 (1H, s); δ_C: 39.2, 47.5, 49.1, 50.4, 53.6, 94.5, 134.1, 141.2, 154.5, 157.7. MS *m/z* (%): 350 (M^+, 3), 303 (33), 267 (100), 132 (48). *Anal.* Found: C, 37.29; H, 4.30; N, 20.31; S, 9.21%. Calcd. for $C_{11}H_{16}ClN_5O_4S$: C, 37.77; H, 4.61; N, 20.02; S, 9.17%.

*1-(6-Chloro-3-pyridylmethyl)-2-cyanoimino-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**26**).* A solution of diamine **24** (1.08 g, 4.97 mmol) and *S*,*S*′-dimethyl-*N*-cyanodithioiminocarbonate (0.70 g, 4.82 mmol) in 20 ml of ethanol was refluxed for 20 h. After evaporating the solvent, chromatography on silica gel using $CHCl_3$/ethanol (15:1, v/v) as the eluent gave the product as pale yellow crystals in 17.5% yield (250 mg). Mp: 192–193 °C. IR ν_{max} (KBr): 3135, 2169, 1610, 1559, 1464, 1433, 1313, 1091 cm^{-1}. NMR δ_H ($CDCl_3$): 3.18 (6H, s), 3.25 (2H, m), 3.36 (2H, m), 4.58 (2H, s), 6.54 (1H, s), 7.28 (1H, d, $J = 8.4$), 7.71 (1H, dd, $J = 8.4/2.6$), 8.30 (1H, d, $J = 2.6$); δ_C: 44.0, 48.8, 49.4, 50.9, 93.8, 118.8, 124.5, 130.8, 138.7, 148.9, 151.1, 157.8. MS *m/z* (%): 309 (M^+, 14), 278 (84), 264 (77), 126 (84), 43 (100). *Anal.* Found: C, 47.59; H, 5.00; N, 17.21%. Calcd. for $C_{13}H_{16}ClN_5O_4$: C,47.64; H, 4.92; N, 17.10%.

*1-(6-Chloro-3-pyridylmethyl)-2-nitromethylene-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**27**).* A solution of diamine **24** (2.21 g, 8.59 mmol) and 1,1-bismethylthio-2-nitroethene (1.47 g, 8.88 mmol) in 30 ml of ethanol was refluxed for 16 h. The precipitated crystals were collected and washed with hexane. Yield: 175 mg (6.3%). Mp: 208 °C. IR ν_{max} (KBr): 3130, 1583, 1458, 1429, 1273, 1091 cm^{-1}. NMR δ_H ($CDCl_3$): 3.27 (6H, s), 3.42 (2H, m), 3.52 (2H, m), 4.44 (2H, s), 6.54 (1H, s), 7.38 (1H, d, $J = 8.4$), 7.56 (1H, dd, $J = 8.4/2.6$), 8.31 (1H, d, $J = 2.6$), 10.84 (1H, bs); δ_C: 42.8, 48.9, 51.0, 53.3, 93.4, 98.3, 124.8, 128.9, 136.9, 147.9, 151.6, 154.3. MS *m/z* (%): 329 (M^+, 38), 282 (93), 126 (100). *Anal.* Found: C, 47.29; H, 5.30; N, 17.30%. Calcd. for $C_{13}H_{17}ClN_4O_4$: C, 47.49; H, 5.21; N, 17.04%.

*2-(Tetrahydrofuran-3-ylmethyl)-2-nitromethylene-5,5-dimethoxy-1,4,5,6-tetrahydropyrimidine (**28**).* A solution of diamine **25** (1.08 g, 4.97 mmol) and 1,1-bismethylthio-2-nitroethene (0.85 g, 5.20 mmol) in 20 ml of ethanol was refluxed for 20 h. The solvent was distilled off and subsequent column chromatography (silica gel) of the residual semisolid with $CHCl_3$/ethanol (20:1 and then 10:1, v/v) afforded 570 mg (40% yield) of a product as colorless crystals with mp 132 °C. IR ν_{max} (KBr): 3159, 2944, 1576, 1429, 1306, 1202, 1133, 1118, 1086, 1049, 759 cm^{-1}. NMR δ_H ($CDCl_3$): 1.60 (1H, m), 2.10 (1H, m), 2.64 (1H, m), 3.15 (1H, m), 3.27 (1H, m), 3.29 (6H, s), 3.40 (2H, m), 3.48 (2H, m), 3.58 (1H, m), 3.77 (2H, m), 3.93 (1H, m), 6.66 (1H, s), 10.86 (1H, bs); δ_C: 29.6, 38.2, 43.1, 48.7, 67.3, 70.4, 93.2, 98.4, 154.0. MS *m/z* (%): 289 (M^+, 45), 242 (68), 88 (74), 43 (100). *Anal.* Found: C, 50.29; H, 7.30; N, 14.30%. Calcd. for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63%.

Biological tests.

Chemicals. Compounds **2**,[15] **3**/**4**,[16] and **31**/**32**[17] were prepared according to the reported procedures. Reagent-grade piperonyl butoxide (PB) purchased from Tokyo Kasei Kogyo Co. (Tokyo, Japan) was used as an inhibitor of oxidative metabolism. NIA 16388 (propargyl propyl benzenephosphonate; NIA) was the same as the sample used in our previous studies.[18–22] NIA originally is an inhibitor of the hydrolytic metabolism of pyrethroids.[23]

Insecticidal tests against the green peach aphid (Myzus persicae). Paper towels were placed on the base of a cage and watered. On them, wet rice seeds were sown, and the cage stored for germination in the dark at

Table 1. Biological Activities of the Tested Compounds

Compound no.	Spray insecticidal rating (%)[a,b] 20	4	0.8	0.16	Injection insecticidal activity MLD (μmmol)[b] Alone	+(PB + NIA)	Neuroblocking potency[b] BC (mM)
2	100	100	100	90	0.015	9.6×10^{-5}	0.0045
18	100	100	90	60	≫0.38	0.19	~0.56
19	100	100	60	50	≫0.34	0.24	≫0.56
20	90	90	60	30	≫0.36	~0.36	≫0.56
21	100	100	60	40	≫0.36	~0.36	≫0.54
26	100	60	60	20	≫0.40	≫0.40	~0.62
27	90	60	0	NT	≫0.44	0.35	~1.0
28	60	0	NT	NT	≫0.36	≫0.36	≫0.54
3	60	0	NT	NT	NT	NT	NT
4	40	0	NT	NT	NT	NT	NT
31	0[c]	NT	NT	NT	>0.40[d]	>0.40[d]	>0.65[d]
32	100	100	100	100	0.0051[d]	0.0051[d]	0.0085[d]

[a]The percentage killing rate at three specified doses in ppm for *Myzus persicae* 7 d after the treatment. See the text for the details.
[b]MLD, minimum lethal dose; BC, neuroblocking concentration. See the text for the details. NT, not tested.
[c]60% at 100 ppm.
[d]Ref. 36.

30 °C for 4 d. After storage, the etiolated small rice plants about 2 cm tall were sprayed from above with an aqueous solution of a test compound. The concentration of the compound was adjusted in four stages from 20 to 0.16 ppm. After spraying, ten nymphs were released on the plants, and the mortality was determined in % after 7 d.

Insecticidal test against the American cockroach. The insecticidal assay against the male adult American cockroach, *Periplaneta americana* L., was conducted as previously described.[18–22] Various volumes (1–10 μl) of each compound dissolved in methanol containing dimethyl sulfoxide (DMSO) were injected into the abdomen of a cockroach. Organic solvents alone in this range did not have any toxic effect. Details of the dosage were fundamentally the same as described previously.[18,22] The dose was varied in stages of 1.25 times in moles. In some experiments, a methanol solution (1 μl) containing PB (50 μg) and NIA (50 μg) was injected 1 h before injection of the test compound. The metabolic inhibitors in these amounts did not have any toxic effect. Three insects were used to test each dose of each compound and were kept at 22–25 °C for 24 h after the injection. The minimum dose at which two of three insects were killed was taken as the minimum lethal dose (MLD) in mol. Paralyzed insects were counted as dead. The MLD values for the test compounds are listed in Table 1. Each value is the mean of at least two experiments with a deviation of 0.64–1.6 times.

Neurophysiological assay. A neurophysiological test of the compounds was conducted as previously described.[19–22] In brief, a nerve preparation containing the abdominal fifth and sixth ganglia of a male adult American cockroach was excised and placed in a saline solution. One of two bundles of the nerve cord was taken up from the thoracic side with saline into a glass tube, in which a silver wire was set as an electrode. As the reference electrode, another wire was set outside the cut end of the tube. The silver wires were thinly coated with silver chloride. The number of spontaneous discharges that were larger than approximately 15 μV was consecutively counted with a pulse counter (MET-1100, Nihon Kohden, Tokyo, Japan) for every 30-sec period. The frequency was usually quite high in a few minutes after setting, and then normally subsided. When the frequency had decreased to a range of 30–400 counts per 30 sec in about 2 min, the saline solution was exchanged for another saline solution containing a test compound dissolved in methanol solution containing DMSO. The final concentration of the organic solvent was lower than 1% (v/v), which did not affect the nerve activity. Measurements were conducted at 22–25 °C. The evaluation of the neuroblocking activity was based on the previously reported procedure.[21,22] The time when the number of firing first decreased to fewer than 10 counts per 30 s, which is defined as t in min, was determined. The effect on the frequency and the time to subside depended on the concentration of the compound (Fig. 3). Similar measurements were conducted at two concentrations for each compound, more than three nerve preparations being used for each concentration of each compound. A concentration-response relationship for each compound (data not shown) enabled the concentration required to reach 1 in terms of $\log t$ was determined and defined as BC (in M). The BC values are listed in Table 1.

Results and Discussion

The synthetic scheme is depicted in Fig. 2. The key intermediate, 1,3-diaminoacetone dimethyl acetal (**16**), was prepared from dihydroxyacetone dimer **11** in four steps. The S_N2 type of substitution of the bis-tosylate (**14**) to azides (**15**) was extremely sluggish in this process. The conventional procedure in refluxing acetone, ethanol, or acetonitrile with or without crown ether resulted in recovery of the starting tosylate, and even such harsh conditions as 120 h of heating at 120 °C in

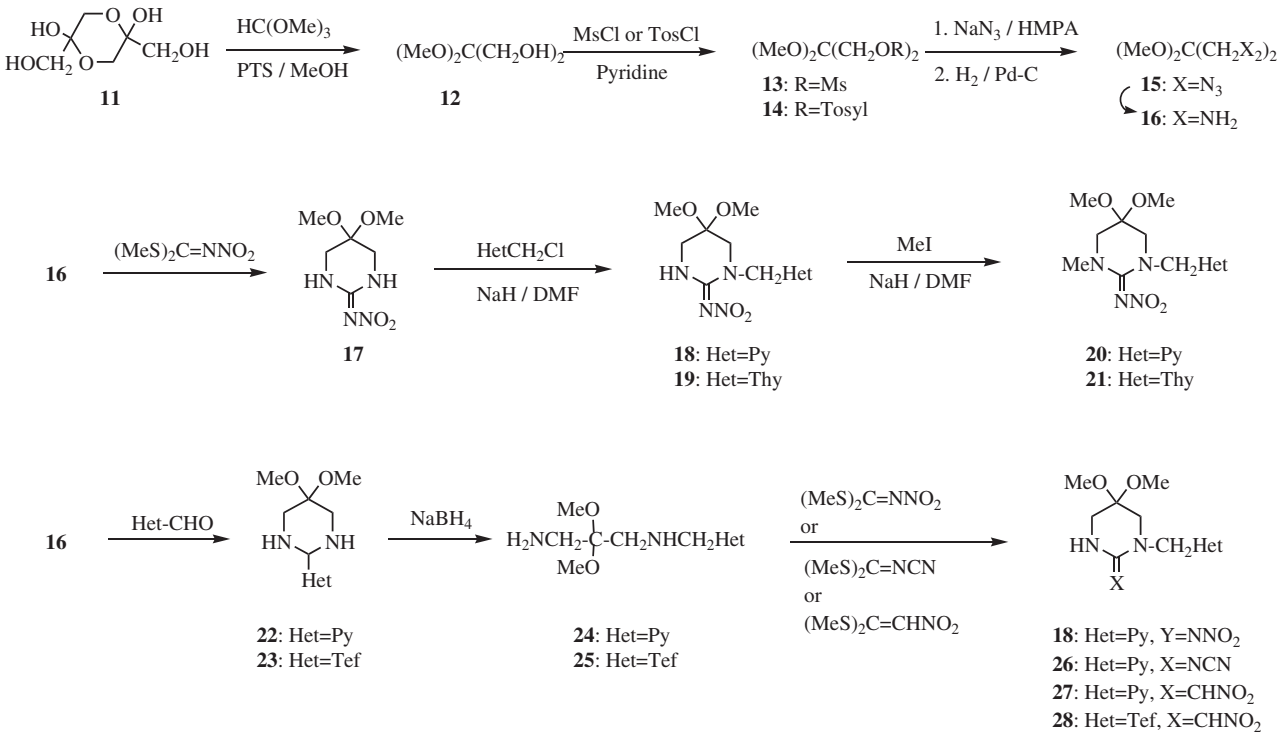


Fig. 2. Preparation Scheme for 1,3-Diazacyclohexane Acetals.
See Fig. 1 for the structural abbreviations of Py, Thy and Tef.

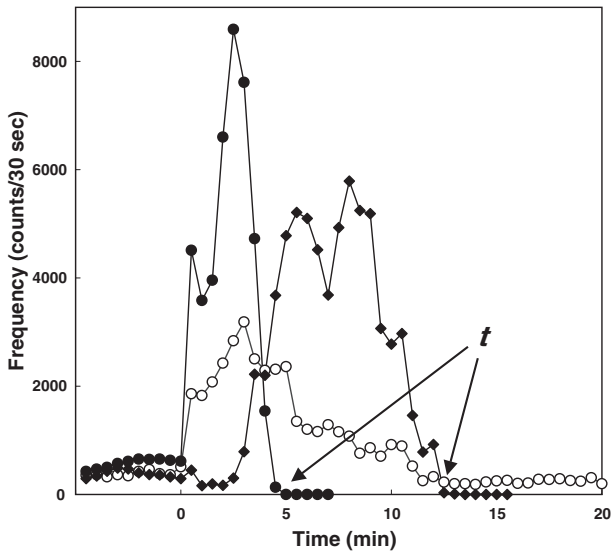


Fig. 3. Time Course Characteristics for the Effect of Compounds **2** and **18** on the Spontaneous Discharge in Excised Central Nerve Cords of American Cockroaches.

After counting for 5 min, the nerve preparations were applied with compounds **2** (◆, 1.3×10^{-6} M; ●, 5.0×10^{-6} M) and **18** (○, 5.7×10^{-4} M) at zero min.

DMF only gave a 10% yield of the diazide. We optimized the process by using bis-mesylate **13** as the substrate and HMPA as the solvent, and we could obtain desired product **15** in a 60% yield after 60 h at 120 °C. Hydrogenolysis of this diazide to diamine **16** proceeded smoothly. This straightforward approach to functionalized 1,3-diaminopropane will provide practical access to a precursor for therapeutically interesting imidazobenzodiazepines,[24] 1,3-diazacyclohexanes[25] and antitumor cisplatine-related metal ligands.[26] The final hetarylmethyl 1,3-diazacyclohexanone acetals were prepared by two routes. The first route started with 2-nitroiminotetrahydropyrimidine acetal (**17**) that was in turn prepared by the condensation of *N*-nitroimidodithiocarbonate[27] with diamine **16**. The free NH of **17** was readily substituted with 6-chloronicotinyl chloride and chlorothiazolylmethyl chloride using sodium hydride as the base, respectively giving **18** and **19**, and further another NH was methylated without difficulty. The second route made use of 1-(6-chloronicotinyl)- or 1-(tetrahydrofuranylmethyl)-1,3-diaminopropane acetal **24** or **25** as the precursor. The protocol starting with dehydrative condensation of hetarylaldehyde with 1,3-diaminopropane in refluxing benzene and followed by reduction of the formed C=N bond has been applied as a routine method for *N*-hetarylmethyl-substituted 1,3-diamine.[15,28] However, with 1,3-diamino-2,2-dimethoxypropane as the substrate, 2-hetaryl-hexahydropyrimidines (**22**/**23**) were formed instead of the expected imine. Variation of the edduct ratio or replacement with other solvents did not recede the step to the intramolecular cyclization. Fortunately, however, we found that hexahydropyrimidines (**22**/**23**) could also be reduced to 1,3-diaminopropane derivatives (**24**/**25**) with sodium borohydride, although very slowly. The final reactions for compound(s) **18** (or **26**–**28**) proceeded without difficulty.

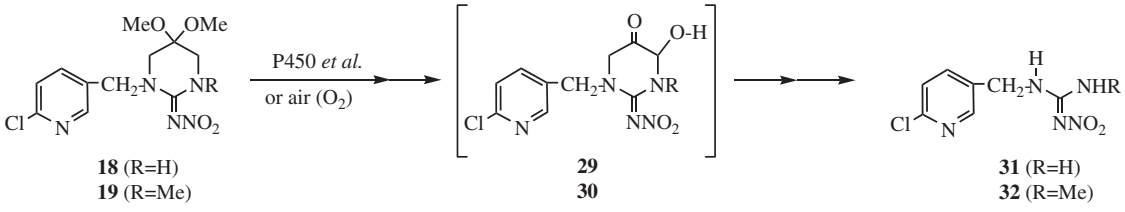
Neonicotinoid is especially effective against chewing and sucking insects.[29] We chose in this study the green peach aphid (*Myzus persicae*), a target insect for this insecticide class, to evaluate the insecticidal activity of the present compounds. Spray treatment with the tested acetals was highly insecticidal against aphids at 20 ppm after seven days, except for the tetrahydrofuranyl derivative (**28**) which had modest activity. The nitroimine derivatives (**18**–**21**) showed the most appreciable insecticidal effect at as low a concentration as 4–0.8 ppm, although they did not match the effect of compound **2** at 0.16 ppm. This was in contrast to the far lower activity of the 5,5-dimethyl (**3**) and 5-methoxy derivatives (**4**). The higher activity of the dimethyl acetals than compound **3** bearing a likely steric increment or compound **4** carrying a similar hydrophilic element suggests that a certain property of the carbonyl-protecting group would have been involved in the exhibition.

The insecticidal activity by injecting into the insect body can be evaluated after regulating factors involving decomposition in the environment and the ease of cuticular penetration. The activity determined by this injection method with the cockroach for acetals **18**–**21** and **26**–**28** without metabolic inhibitors was much more than 20 times lower than that of the prototype (**2**). It is not clear whether the lower activity exhibited by injection was related to low hydrolysis rates of the acetals in the insect during the testing period of 24 h.

Insecticides are metabolized by various enzyme systems. A recent study on neonicotinoids using recombinant cytochrome P450 (CYP450) isozymes showed that reduction at the nitroimine substituent is the main metabolic process for imidacloprid, and the oxidation at the imidazolidine moiety is a side path.[30,31] On the other hand, there are some metabolic inhibitors that prevent or minimize the deactivation of an insecticide by enzymes and generally enhance the activity exhibited when neat. NIA and PB are known as respective inhibitors of the hydrolytic and oxidative metabolism of pyrethroids,[23] and their synergistic effect is also apparent in neonicotinoids.[19–22] We thought that these synergists might also inhibit the hydrolysis of these acetals to ketones, thus retaining the low activity. However, the addition of PB and NIA brought about an activity increase as was obvious in compounds **18**, **19** and **27**, and recognizably so in compounds **20** and **21**. These results suggest that the synergists mainly interfered with the metabolic attack occurring at the nitroimino and analogous electron-withdrawing group of these compounds, rather than with any hydrolysis of the acetal.

Neonicotinoid compounds give a characteristic nerve impulse pattern from the action at the insect nicotinic acetylcholine receptor, *i.e.* enhancement of spontaneous firing followed by the blockage of neural activity.[19–22] Figure 3 relates the frequency of spontaneous discharges in the excised central nerve cords of American cockroaches over time resulting from the treatment with compounds **2** and **18**. The two-phase characteristics of the initially increasing and then decreasing were clearly apparent. With compound **2**, the frequency decreased to zero around 13 min after the start of treatment at 1.3×10^{-6} M. With compound **18**, however, some discharges were still counted even 20 min after the start of treatment at 5.7×10^{-4} M, this being the highest concentration tested. By estimating in a similar manner to that for the previous electrophysiological experiments,[21,22,32–34] the blocking concentration for compounds **18**, **26** and **27** was almost the same in a range of 0.6–1.0 mM. The much larger values than for prototype **2** of 4.5 μM are due to the evidently weak neuroblocking activity of these acetals. The other acetals were such weak blockers that we could not identify any definite nerve-blocking phenomenon at as high a concentration as 0.5 mM in this 30-min measurement period.

We have already observed the almost parallel relationship between the activities against sucking insects and the estimates using American cockroaches.[20,29] The present acetal derivatives were generally weak in insecticidal activity by injection as well as in neuroblocking activity. However, it is notable that a few of them were fairly high in this insecticidal estimates toward aphids 7 days after spraying. These biological results suggest that the intrinsic insecticidal activity of the acetals is weak and some substances enhanced this activity during the testing period. As depicted in eq. 2 in Fig. 1, acetal hydrolysis and the subsequent 1,3-diacyl type of cleavage leading to active compound, *e.g.* **32**, will be a plausible transformation under such greenhouse conditions. Another possible decomposition process is based on the well-documented path for the dealkylation metabolism of alkylamines through oxidation (hydroxylation) at the α-methylene,[35] as depicted in Fig. 4. However, the obviously lower aphidicidal activity of compound **31** than of cyclic acetal **18**[36] would



18 (R=H)
19 (R=Me)

29
30

31 (R=H)
32 (R=Me)

Fig. 4. Alternative Possible Cleavage Path of Acetals **18**/**19** to **31**/**32**.

suggest either no such cleavage or no contribution to the activity. There would also be a question of whether the ketone itself was responsible for the biological activity. Trials to deprotect the acetal group to the ketone in various acidic solutions at various temperatures resulted in recovery of the acetal or in an intractable residual reaction mixture. Deprotection under neutral or milder conditions according to the published protocols[6] also failed. Alternatively, oxidation of the known 5-hydroxy-1,3-diazacyclohexane[16] has not succeeded either so far.

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