Synthetic procedure for modifying the amine part of carpropamid: Changing 4-chlorophenethylamine to alkyl, alicyclic, and substituted phenylalkylamines

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Compounds of the 4-chlorophenethyl amine part of carpropamid were replaced with alkyl, cycloalkyl and substituted phenylalkyl amines. The amines were obtained from the corresponding ketoximes using a reduction system of sodium borohydride with molybdenum oxide as the additive. © Pesticide Science Society of Japan

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Introduction

The emergence of fungus resistant to carpropamid (1), a melanin biosynthesis inhibitor, was recently reported and the cause was identified as a mutation of the valine residue to methionine in scytalone dehydratase (SDH).1,2) Carpropamid enters the SDH biosynthesis inhibitor, was recently reported and the cause was identified as a mutation of the valine residue to methionine in scytalone dehydratase (SDH).1,2) Carpropamid enters the SDH pathway for the starting alkyl, cycloalkyl and aralkyl tyylethylamine3) and the 3-(4-chlorophenyl)propylamine, 1-phenylethylamine and 1-(4-chlorophenyl)ethylamine are commercially available and used without further purification. 1-Methyl-4,4,4-trifluoropropylamine5) and 1-cyclopropyl-4-chlorophenethylamine (Fig. 1). This note describes the preparative details are not accessible. We prepared these amines from the corresponding acetylcycloalkane oximes6) as well as a new amine, 1-(4-chlorophenyl)propylamine, by slightly modifying the reported procedure (Fig. 2).

Typical reduction procedure: To a mixture of acetylcyclohexane oxide (1.29 g, 0.091 mol) and MoO3 (1.81 g, 0.126 mol) in 60 ml of methanol in an ice-water bath was added powdered NaBH4 (3.38 g, 0.914 mol) portionwise. An exothermic reaction occurred with vigorous gas evolution about 30 min after the addition. When the exothermic reaction ceased, the cooling bath was set aside and the reaction mixture was stirred at ambient temperature for 5 hr. The mixture was allowed to stand overnight. After separating the supernatant layer by decantation, the rest of the mixture was filtered through a Celite bed with weak suction and the bed washed with methanol. The combined methanol solution was acidified with conc. HCl and the precipitated solid was filtered off. The methanol was distilled off and the residual solid was dissolved in water and, after confirming that the solution was acidic, washed several times with hexane. The aqueous phase was cooled in an ice bath and alkalized to pH 10–12 with solid NaOH, and extracted with ether several times. The combined ether phase was dried over solid KOH. Following the careful distillation of ether, the fraction of 1-cyclohexylethylamine was collected. Yield: 680 mg (59%). Bp. 130–135°C/760 mmHg (34°C/30 mmHg).10


1-(4-Chlorophenyl)propylamine. Oxime was prepared by heating a mixture of 4-chlorophenylpropanone (2.40 g, 14 mmol), hydroxylamine · HCl (2.50 g, 39.4 mmol) and dry pyridine (2.5 ml) in dry ethanol (25 ml) for 3 hr at 80°C. After the evaporation of ethanol, the residual liquid was partitioned between water and hexane, and the hexane layer was separated and dried. The hexane was distilled off and the residue that crystallized was rinsed with a small amount of chilled hexane. Yield: 2.34 g (90%). Mp. 67–68°C. IR (KBr) cm−1: 1495, 1090, 972, 920. 1H-NMR δH (CDCl3): 1.16 (3H, t, J=7.4Hz, CH2CH3), 2.80 (2H, q, J=7.4Hz)
J = 7.4 Hz, CH₂CH₃), 7.35 (2H, d, J = 8.6 Hz, Phenyl), 7.54 (2H, d, J = 8.6 Hz, Phenyl), 9.51 (1H, bs, OH). EI-MS m/z (%): 183 (M⁺, 100), 166 (63), 138 (78). From oxime (2.20 g, 12 mmol) was obtained 1.06 g of amine in 52% yield by the above reduction procedure. Bp. 72–75/24 mmHg. IR (film) cm⁻¹: 3420. ¹H-NMR dH (CDCl₃): 1.14 (3H, t, J = 7.7 Hz, CH₂CH₃), 1.68 (2H, m, CH₂CH₃), 3.80 (1H, t, J = 7.0 Hz, CH), 7.24 (2H, d, J = 8.2 Hz, Phenyl), 7.28 (2H, d, J = 8.2 Hz, Phenyl). EI-MS m/z (%): 169 (M⁺, 3), 166 (71), 153 (42), 138 (100).

The amides were prepared according to the described procedure. The spectral data of the products are as follows:

N-Isopropyl-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (2). Mp. 99°C. IR (KBr) cm⁻¹: 1645. ¹H-NMR δH (CDCl₃): 1.14 (3H, t, J = 7.7 Hz, CH₂CH₃), 1.68 (2H, m, CH₂CH₃), 3.80 (1H, t, J = 7.0 Hz, CH), 7.24 (2H, d, J = 8.2 Hz, Phenyl), 7.28 (2H, d, J = 8.2 Hz, Phenyl). EI-MS m/z (%): 237 (M⁺, 16), 222 (100).

N-(sec-Butyl)-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (3). Mp. 111°C. IR (KBr) cm⁻¹: 1645. ¹H-NMR δH (CDCl₃): 0.92–1.01 (6H, overlap), 1.16–1.20 (6H, overlap), 1.55 (3H, overlap, CH₃CH₂CH₂+1-cyclopropyl CH₂CH₂), 1.97 (1H, m, 1-cyclopropyl CH₂CH₂), 2.21 (1H, q, J = 6.6 Hz, 3-cyclopropyl-H), 4.15 (1H, m, CH(CH₃)₂), 5.55 (1H, bs, NH). EI-MS m/z (%): 263 (M⁺, 3), 180 (59), 69 (100).

N-(1-Cyclobutylethyl)-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (6). Mp. 127–128. IR (KBr) cm⁻¹: 1642. ¹H-NMR δH (CDCl₃): 0.92–1.01 (6H, overlap), 1.16–1.20 (6H, overlap), 1.55 (3H, overlap, CH₃CH₂CH₂+1-cyclopropyl CH₂CH₂), 1.97 (1H, m, 1-cyclopropyl CH₂CH₂), 2.21 (1H, q, J = 6.6 Hz, 3-cyclopropyl-H), 4.03 (1H, m, NCHCH₂), 5.42 (1H, bs, NH). EI-MS m/z (%): 277 (M⁺, 6), 180 (39), 55 (100).

N-(1-Cyclohexylethyl)-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (6). Mp. 127–128. IR (KBr) cm⁻¹: 1642. ¹H-NMR δH (CDCl₃): 0.92–1.01 (6H, overlap), 1.16–1.20 (6H, overlap), 1.55 (3H, overlap, CH₃CH₂CH₂+1-cyclopropyl CH₂CH₂), 1.97 (1H, m, 1-cyclopropyl CH₂CH₂), 2.21 (1H, q, J = 6.6 Hz, 3-cyclopropyl-H), 4.03 (1H, m, NCHCH₂), 5.42 (1H, bs, NH). EI-MS m/z (%): 277 (M⁺, 6), 180 (39), 55 (100).
N-[2-(4-Chlorophenyl)-1-methylthethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (16). Mp. 112–115°C. IR (KBr) cm⁻¹: 1635. ¹H-NMR δH (CDCl₃): 0.71–0.91 (9H, m, 1-cyclopropyl-CH₂CH₃), 1.12–1.18 (6H, overlap, 3-cyclopropyl-CH₂+CH₂CH₂CH₂), 1.46 (1H, m, CH₂CH₃), 1.71–2.11 (1H, m, 3-cyclopropyl-CH₃), 2.14 (1H, m, CH₂CH₃), 2.58–2.94 (2H, m, CH₂CH₂), 4.31 (1H, m, CH₂CH₂NH), 5.53–5.62 (1H, m, NH), 7.11–7.26 (4H, m, phenyl ring). EI-MS m/z (%): 347 (M⁺, 1), 179 (100).

N-[2-(4-Fluorophenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (17). Mp. 123°C. IR (KBr) cm⁻¹: 1635. ¹H-NMR δH (CDCl₃): 0.90 (3H, t, J = 7.4Hz, CH₂CH₃), 1.19 (3H, d, J = 6.3Hz, 3-cyclopropyl-CH₃), 1.52 (1H, m, CH₂CH₃), 1.85 (1H, m, CH₂CH₃), 2.18 (1H, q, J = 6.3Hz, 3-cyclopropyl-H), 2.85 (2H, m, NCH₂CH₃), 3.58 (2H, m, NCH₂CH₃), 5.82 (1H, bs, NH), 7.15 (2H, d, J = 8.6Hz, meta H to CH₂), 7.28 (2H, d, J = 8.6Hz, ortho H to CH₂). EI-MS m/z (%): 317 (M⁺, 28), 122 (100).

N-[2-(2-Chlorophenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (20). Mp. 140–142°C. IR (KBr) cm⁻¹: 1640. ¹H-NMR δH (CDCl₃): 0.90 (3H, t, J = 7.4Hz, CH₂CH₃), 1.19 (3H, d, J = 6.6Hz, 3-cyclopropyl-CH₂), 1.52 (1H, m, CH₂CH₃), 1.90 (1H, m, CH₂CH₃), 2.19 (1H, q, J = 6.6Hz, 3-cyclopropyl-H), 3.01 (2H, t, J = 7.1Hz, NCH₂CH₃), 3.66 (2H, m, NCH₂CH₃), 5.97 (1H, bs, NH), 7.16–7.37 (4H, m, benzene ring). EI-MS m/z (%): 333 (M⁺, 36), 139 (100).

N-[2-(3-Chlorophenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (21). Mp. 111–112°C. IR (KBr) cm⁻¹: 1630. ¹H-NMR δH (CDCl₃): 0.91 (3H, t, J = 7.3Hz, CH₂CH₃), 1.19 (3H, d, J = 6.7Hz, 3-cyclopropyl-CH₂), 1.52 (1H, m, CH₂CH₃), 1.87 (1H, m, CH₂CH₃), 2.19 (1H, m, 3-cyclopropyl-H), 2.84 (2H, m, NCH₂CH₃), 3.59 (2H, m, NCH₂CH₃), 5.88 (1H, bs, NH), 7.10–7.29 (4H, m, benzene ring). EI-MS m/z (%): 333 (M⁺, 74), 179 (100).

N-[2-(3,4-Dichlorophenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (23). Mp. 110°C. IR (KBr) cm⁻¹: 1630. ¹H-NMR δH (CDCl₃): 0.92 (3H, t, J = 7.3Hz, CH₂CH₃), 1.20 (3H, d, J = 6.6Hz, 3-cyclopropyl-CH₂), 1.53 (m, CH₂CH₃), 1.87 (1H, m, CH₂CH₃), 2.18 (1H, q, J = 6.6Hz, 3-cyclopropyl-H), 2.84 (2H, m, NCH₂CH₃), 3.58 (2H, m, NCH₂CH₃), 5.90 (1H, bs, NH), 7.06 (1H, m, benzene ring), 7.32 (m, 1H, benzene ring), 7.37 (1H, m, benzene ring). EI-MS m/z (%): 367 (M⁺, 44), 172 (100).

N-[2-(4-Bromophenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (24). Mp. 144–146°C. IR (KBr) cm⁻¹: 1630. ¹H-NMR δH (CDCl₃): 0.90 (3H, t, J = 7.6Hz, CH₂CH₃), 1.19 (3H, d, J = 6.6Hz, 3-cyclopropyl-CH₂), 1.52 (m, CH₂CH₃), 1.84 (1H, m, CH₂CH₃), 2.18 (1H, q, J = 6.6Hz, 3-cyclopropyl-H), 2.84 (2H, m, NCH₂CH₃), 3.58 (2H, m, NCH₂CH₃), 5.79 (1H, bs, NH), 7.11 (2H, d, J = 8.1Hz, ortho H), 7.43 (2H, d, J = 8.1Hz, meta H). EI-MS m/z (%): 379 (M⁺, 34), 182 (100).

N-[2-(4-Methylphenyl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (25). Mp. 118–119°C. IR (KBr) cm⁻¹: 1640. ¹H-NMR δH (CDCl₃): 0.90 (3H, t, J = 7.3Hz, CH₂CH₃),
Results and Discussion

Alkyl amines can be prepared in various ways. The reduction of the corresponding oximes is a representative route and seemed suitable for the present secondary alkyl amines because the starting ketones are readily accessible. Lithium aluminum hydride is often used for this transformation, but it is sometimes difficult to separate from the concomitant rearranged products in the case of phenylketone oximes. Sodium borohydride does not reduce oximes under ambient conditions; however, the reactivity enhancement has been elaborated by adding Lewis acids like TiCl₄, CoCl₂, ZrCl₄, FeCl₃, NiCl₂, or MoO₃. Among the above additives, Ipaktschi’s procedure using MoO₃ gave the best results for the present oximes. The last step to the final amides proceeded smoothly according to the reported protocol, and the structures were confirmed by IR, NMR and MS spectra.

This note showed that the sequence from the ketone via oxime to α-alkyl amine is a suitable scheme for the necessary derivatives of modified carpropamid.

References