# SOME NEW SYMPATHOMIMETIC AMINES: *N*-CYCLOALKYL DERIVATIVES OF 1,2,3,4-TETRAHYDRO-2-NAPHTHYLAMINE AND OF NORADRENALONE*

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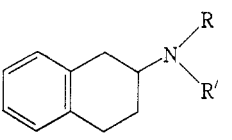
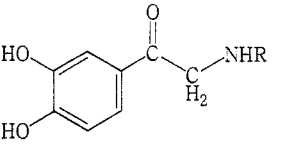
Several cycloalkyl derivatives of 1,2,3,4-tetrahydro-2-naphthylamine (I; R = cyclopentyl, R′ = H or $CH_3$; R = cyclobutylmethyl, R′ = H) have been synthesized for the purpose of studying their sympathomimetic or sympatholytic actions, and possible antagonism to serotonin and histamine, following earlier findings with analogous compounds.[1–3] The related amides [I; R = cyclobutylcarbonyl ($COC_4H_7$), cyclopropylcarbonyl ($COC_3H_5$), pivaloyl ($COC(CH_3)_3$), R′ = H] might also be expected, from the findings of Marini-Bettolo *et al.*[4] on similar amides, to have sympatholytic and hypotensive action.




(I)




(II)

Some *N*-cycloalkyl noradrenalone derivatives (II; R = cyclobutyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydro-2-naphthyl, and *p*-acetylphenyl) were also prepared as potential sympathomimetic agents for pharmacological study. The *N*-cyclohexyl- and *N*-cyclopentyl-noradrenalones have been previously described by Corrigan *et al.*[5]

## *Experimental*

Melting points were taken on a Kofler block and are uncorrected. Infrared spectra were determined in Nujol mulls using a Perkin–Elmer Infracord spectrophotometer. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

(*a*) *N-Cyclopentyl-1,2,3,4-tetrahydro-2-naphthylamine*

A mixture of 1,2,3,4-tetrahydro-2-naphthylamine (3·7 g) and cyclopentyl bromide (1·9 g) in dry xylene (20 ml) was refluxed for 30 hr. The precipitated amine hydrobromide (2·4 g, 86%) was filtered, the xylene evaporated from the filtrate, and the residue distilled. The product (1·66 g) had b.p. 126°/0·7 mm, and with ethereal HCl deposited a *hydrochloride*, crystallized from ethanol/ether, m.p. 178–180° (Found: C, 71·6; H, 8·9; N, 5·7. $C_{15}H_{22}ClN$ requires C, 71·6; H, 8·8; N, 5·6%).

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[1] Cymerman Craig, J., Moore, B., and Ritchie, E., *Aust. J. Chem.*, 1959, **12**, 447.
[2] Cymerman Craig, J., Moore, B., and Temple, D. M., *Aust. J. Chem.*, 1960, **13**, 463.
[3] Pennefather, J. N., and Thorp, R. H., *Archs int. Pharmacodyn. Thér.*, 1959, **121**, 355.
[4] Marini-Bettolo, G. B., Chiavarelli, S., and Bovet, D., *Rc. Ist. sup. Sanità*, 1952, **15**, 767.
[5] Corrigan, J. R., Langermann, M. J., and Moore, M. L. *J. Am. chem. Soc.*, 1949, **71**, 530.

(*b*) N-*Cyclopentyl-1,2,3,4-tetrahydro*-N-*methyl-2-naphthylamine*

The above amine (1·66 g) was methylated in the usual manner[1] with formaldehyde and formic acid. The product had b.p. 117–128°/0·25 mm, and with ethereal HCl gave a *hydrochloride* as prisms of monohydrate from ethanol/ether, m.p. 144–146° (Found: C, 67·8; H, 9·2; N, 5·15. $C_{16}H_{24}ClN,H_2O$ requires C, 67·8; H, 9·2; N, 5·0%).

(*c*) N-(*1,2,3,4-Tetrahydro-2-naphthyl*)*cyclobutanecarboxamide*

A solution of cyclobutanecarboxylic acid chloride (1·2 g, 0·01 mole), prepared from cyclobutanecarboxylic acid[6] with thionyl chloride, and 1,2,3,4-tetrahydro-2-naphthylamine (2·9 g, 0·02 mole) in chloroform (30 ml) was refluxed for 2 hr. The mother liquor from the precipitated amine hydrochloride yielded on evaporation a crystalline residue (2·25 g) which recrystallized from light petroleum as white *prisms* (1·1 g), m.p. 105–106° (Found: C, 78·6; H, 8·4; N, 6·7. $C_{15}H_{19}NO$ requires C, 78·6; H, 8·4; N, 6·1%). $\nu_{max}$ 3250, 1655 cm$^{-1}$.

(*d*) N-*Cyclobutylmethyl-1,2,3,4-tetrahydro-2-naphthylamine*

The above amide (0·9 g) was reduced with lithium aluminium hydride (0·3 g) in anhydrous ether. The reduction product with ethereal HCl formed a *hydrochloride* (0·65 g) which recrystallized from ethanol as white leaflets, m.p. 255–257° (Found: C, 71·2; H, 8·5; N, 5·8. $C_{15}H_{22}ClN$ requires C, 71·55; H, 8·8; N, 5·6%). $\nu_{max}$ 3350, 1590 cm$^{-1}$.

(*e*) N-(*1,2,3,4-Tetrahydro-2-naphthyl*)*cyclopropanecarboxamide*

A mixture of cyclopropylcarboxylic acid chloride (1·05 g, 0·01 mole), 1,2,3,4-tetrahydro-2-naphthylamine (1·47 g, 0·01 mole) and pyridine (0·8 g, 0·01 mole) in chloroform (15 ml) was refluxed for 2 hr. The mother liquor from the hydrochloride precipitate was washed with dilute HCl, $Na_2CO_3$ solution, and water, and evaporated. The residue crystallized as white *needles* (0·87 g) from light petroleum, m.p. 132–135° (Found: C, 78·1; H, 8·0; N, 6·5. $C_{14}H_{17}NO$ requires C, 78·2; H, 7·9; N, 6·8%). $\nu_{max}$ 3250, 1660, 1035 cm$^{-1}$.

(*f*) *1,2,3,4-Tetrahydro*-N-*pivaloyl-2-naphthylamine*

A mixture of pivalic acid chloride (2·4 g, 0·02 mole), 1,2,3,4-tetrahydro-2-naphthylamine (2·94 g, 0·02 mole), and pyridine (1·6 g, 0·02 mole) in chloroform (20 ml) was refluxed for 1 hr, and worked up as in (*e*). The residue (2·1 g) recrystallized from light petroleum as white needles (1·0 g), m.p. 117–120° (Found: C, 77·5; H, 9·0; N, 6·4. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·1 N, 6·1%). $\nu_{max}$ 3280, 1660 cm$^{-1}$.

(*g*) *Cyclobutylamine Salt of 4-Chloroacetylcatechol*

A solution of cyclobutylamine (2·9 g) in isopropanol (20 ml) was added slowly with stirring to a solution of 4-chloroacetylcatechol (3·7 g) in isopropanol (50 ml). The amine salt of the phenol precipitated immediately, and was filtered and washed with ether, to give off-white *prisms* of m.p. 100–104°, 4·75 g (93%) (Found: C, 55·8; H, 6·3; N, 5·2. $C_{12}H_{16}ClNO_3$ requires C, 55·9; H, 6·3; N, 5·4%). $\lambda_{max}$ 206, 232, 280 m$\mu$, $\nu_{max}$ 3210, 3120, 1670, 1600 cm$^{-1}$.

(*h*) *Other Addition Compounds of 4-Chloroacetylcatechol with Primary Amines*

The following salts of 4-chloroacetylcatechol were prepared similarly, using 1 equiv. of amine to one of catechol derivative, which, from alcohol or anhydrous ether, gave an almost quantitative yield of amine salt in each case:

*Cyclohexylamine salt*, m.p. 125–126° (Found: C, 58·6; H, 7·4; N, 5·0. $C_{14}H_{20}ClNO_3$ requires C, 58·8; H, 7·1; N, 4·9%).

*Cyclopentylamine salt*, m.p. 117–119° (Found: C, 57·8; H, 6·8; N, 5·2. $C_{13}H_{18}ClNO_3$ requires C, 57·5; H, 6·7; N, 5·2%).

[6] Heisig, G. B., and Stodola, F. H., *Org. Synth.*, 1955, Coll. Vol. III, 213.

*Cyclopropylamine salt*, m.p. 95–97° (Found: C, 54·6; H, 5·9; N, 5·7. $C_{11}H_{14}ClNO_3$ requires C, 54·2; H, 5·8; N, 5·8%).

*Cyclopropylmethylamine salt*, m.p. 108–110° (Found: C, 53·6; H, 6·2. $C_{12}H_{16}ClNO_3,\frac{1}{2}H_2O$ requires C, 54·0; H, 6·4%).

(*i*) N-*Cyclobutylnoradrenalone Hydrochloride*

The cyclobutylamine salt (0·4 g) of 4-chloroacetylcatechol, prepared as described in (*g*) or (*h*) above, was dissolved in isopropanol (5 ml) and refluxed for 3 hr. It was evaporated to 2·5 ml and chilled, when the *product* (85 mg) precipitated. It was washed with ether and recrystallized from ethanol/ether, m.p. 225–228° (Found: C, 56·1; H, 6·5; N, 5·2. $C_{12}H_{16}ClNO_3$ requires C, 55·9; H, 6·3; N, 5·4%). $\lambda_{max}$ 208, 233, 279, 309 m$\mu$ ($\epsilon$ 7500, 14500, 8600, 7000), $\nu_{max}$ 3120, 1680, 1600 cm$^{-1}$.

The same product resulted when the catechol salt was heated in isopropanol in a sealed tube at 100° for 1·5 hr (yield 28%).

(*j*) N-*Cyclopentylnoradrenalone*

A solution in isopropanol (20 ml) of 4-chloroacetylcatechol (3·0 g) was heated to boiling and cyclopentylamine (4 g) added, with mechanical stirring. After 0·5 hr refluxing the solution was cooled, the resulting precipitate (3·7 g) filtered, washed with isopropanol, and recrystallized from acetone/methanol to give *needles* of the product free base (m.p. 182°), which did not lose water of crystallization on vacuum drying (Found: C, 65·1; H, 7·4; N, 5·5. $C_{14}H_{17}NO_3$ requires C, 66·4; H, 7·3; N, 5·95. $C_{14}H_{17}NO_3,\frac{1}{4}H_2O$ requires C, 65·1; H, 7·4; N, 5·8%). $\lambda_{max}$ 208, 232, 280, 310 m$\mu$ ($\epsilon$ 11300, 9700, 7000, 6700). The free base (0·9 g) with HCl gave the hydrochloride (0·44 g), which crystallized from ethanol/ether and 90% isopropanol to give needles, m.p. 205–207° (lit.[5] 213–214°) (Found: C, 57·8; H, 6·7; N, 5·0. Calc. for $C_{13}H_{18}ClNO_3$: C, 57·5; H, 6·7; N, 5·2%).

(*k*) N-*Cyclohexylnoradrenalone*

Similarly to (*j*), 4-chloroacetylcatechol (3·7 g) with cyclohexylamine (6 ml) yielded a basic product of m.p. 187–188°, which remained hydrated after repeated drying at 100°/1 mm (Found: C, 66·2, 66·2; H, 8·0, 7·6; N, 5·1, 5·0. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6. $C_{14}H_{19}NO_3$, $\frac{1}{4}H_2O$ requires C, 66·25; H, 7·55; N, 5·5%). $\lambda_{max}$ 207, 232, 280, 311 m$\mu$ ($\epsilon$ 9500, 7900, 5600, 5400).

Alternatively, a solution of 3,4-diacetoxy-$\omega$-iodoacetophenone (0·7 g) (prepared from the chloro analogue using KI in methanol), and cyclohexylamine (0·19 g) in acetone (20 ml) was boiled with excess solid $K_2CO_3$ (2·3 g) for 4 hr. The product (117 mg) had m.p. 179–187° (dec.), and an infrared spectrum identical to that of the free base of m.p. 184–187°, described above ($\nu_{max}$ 3420, 1655, 1600 cm$^{-1}$).

Treatment of the free base with ethanolic HCl gave the hydrochloride as white needles from ethanol/ether, m.p. 242–245° (lit.[5] 256–258°) (Found: C, 58·4; H, 6·95; N, 4·7. Calc. for $C_{14}H_{20}ClNO_3$: C, 58·8; H, 7·05; N, 4·9%).

*Hydriodide.*—4-Iodoacetylcatechol (1·0 g) (prepared from 4-chloroacetylcatechol with KI/methanol) in ether (50 ml) was neutralized with cyclohexylamine (0·7 g) to give the insoluble salt (1·15 g), m.p. 111–112°. This addition compound (0·5 g) was suspended in isopropanol (5 ml) which was boiled for 1 hr. On concentration the resulting solution deposited shining cream-coloured *leaflets* (32 mg) which were recrystallized from ethanol/ether, m.p. 239–240° (softened 227°) (Found: C, 44·8; H, 5·5; N, 3·8. $C_{14}H_{20}INO_3$ requires C, 44·6; H, 5·3; N, 3·7%).

(*l*) N-*Cyclopropylnoradrenalone Hydrochloride*

The cyclopropylamine salt of 4-chloroacetylcatechol (1·0 g) was refluxed in isopropanol solution (4 ml) in a current of nitrogen for 3 hr. It was chilled, then concentrated, and the tar-like residue, which showed evidence of decomposition, was triturated in the cold, successively with acetone, methanol, ethanol, and finally with 30% ethanol/ether, in which a yellow solid (0·1 g)

was produced, which crystallized from ethanol/ether (m.p. 180–200°). This was treated in methanol with alcoholic HCl and the hydrochloride crystallized twice from ethanol/ether to give white *needles* (6 mg), m.p. 200–204° (Found: C, 53·6; H, 5·95. $C_{11}H_{14}ClNO_3$ requires C, 54·2; H, 5·8%).

(*m*) N-(*1,2,3,4-Tetrahydro-2-naphthyl*)*noradrenalone Hydrochloride*

A solution of 1,2,3,4-tetrahydro-2-naphthylamine (1·18 g) in 60% ethanol (4 ml) was added dropwise to a solution of 4-chloroacetylcatechol (1·87 g) in ethanol (6 ml) at 5–10°. The resulting solution was heated under reflux for 5 hr, cooled, acidified with HCl, and evaporated at reduced pressure. The residue was triturated with a little ethanol, to give a light-coloured solid (1·0 g) which crystallized from ethanol as *leaflets* of m.p. 219–222° (Found: C, 64·7; H, 6·2; N, 4·0. $C_{18}H_{20}ClNO_3$ requires C, 64·8; H, 6·0; N, 4·2%). $\lambda_{max}$ 231, 274, 308 m$\mu$, $\nu_{max}$ 3500, 3250, 1670 cm$^{-1}$.

(*n*) N-(p-*Acetylphenyl*)*noradrenalone*

Using the same procedure as (*j*), *p*-aminoacetophenone (2·16 g) with 4-chloroacetylcatechol (1·5 g) yielded 1·3 g of white *leaflets*, m.p. 218–219° from isopropanol (Found: C, 67·2; H, 5·3; N, 4·9. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%). $\nu_{max}$ 3300, 1670, 1590 cm$^{-1}$.