Preparation and Anticancer Activity of 2-Diethylaminoethyl-*cis*- and -*trans*-methylcyclohexanecarboxylates

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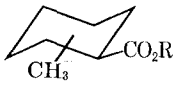
Abstract □ Pure *cis*- and *trans*-methylcyclohexanecarboxylic acids and their 2-diethylaminoethyl esters have been prepared. The latter were isolated as crystalline hydrochloride salts. They were tested for possible anticancer activity.

Keyphrases □ *cis*-, *trans*-Methylcyclohexanecarboxylic acids—synthesis □ 2-Diethylaminoethyl-*cis*-, *trans*-methylcyclohexanecarboxylic esters—synthesis, anticancer activity □ Pharmacological screening—2-diethylaminoethyl-*cis*-, *trans*-methylcyclohexanecarboxylic esters

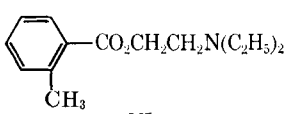
Numerous carboxylic acid esters of tertiary amino alcohols have shown significant pharmacological activity. For instance, the esters of sterically hindered alkyl-substituted benzoic acids have shown anesthetic action (1–5). Similarly, the local anesthetic action of 2-diethylaminoethyl ester hydrochlorides of 1-phenyl and 1-cyclohexanecarboxylic acids is comparable to that of cocaine (6). Investigations of 2-dialkylaminoethyl ester hydrochlorides of various 1-methyl-3-alkyl-cyclohexanecarboxylic acids revealed that these compounds were effective cardiovascular depressants (7). In this paper, the authors report the preparation and anticancer activity of 2-diethylaminoethyl-*cis*- and -*trans*-methylcyclohexanecarboxylate hydrochlorides.

The *cis*- and *trans*-methylcyclohexanecarboxylic acids (I*a*–V*a*) and their 2-diethylaminoethyl esters (I*b*–V*b*), prepared for this investigation, are given in Table I. The three *cis*-methylcyclohexanecarboxylic acids (I*a*, III*a*, and IV*a*) were prepared by the catalytic hydrogenation of the corresponding toluic acids (8, 9). *trans*-2-Methylcyclohexanecarboxylic acid (II*a*) was prepared by heating crotonic acid with 1,3-butadiene in a sealed tube at 175° (10). *trans*-4-Methylcyclohexanecarboxylic acid (V*a*) was prepared by heating the corresponding *cis*-isomer IV*a* in the presence of anhydrous hydrogen chloride (11). However, all attempts to prepare pure *trans*-3-methylcyclohexanecarboxylic acid failed because these procedures gave mixtures of *cis*- and *trans*-isomers which were very difficult to separate. The purity of the acids I*a*–V*a* was established by comparison of boiling points, refractive indexes, and IR spectra with the literature values. The 2-diethylaminoethyl esters of the acids II*a*–V*a* were prepared by the method of Rabjohn (12). This involved heating the potassium salt of the carboxylic acid with 2-chlorotriethylamine in toluene. All attempts to esterify the *cis*-2-methylcyclohexanecarboxylic acid (I*a*) by this method were unsuccessful. Therefore, the acid I*a* was first converted into 2-diethylamino-*o*-toluate (VI). The latter, on catalytic hydrogenation using Adam's catalyst, afforded the 2-diethylaminoethyl-*cis*-2-methylcyclohexanecarboxylate (I*b*). However, all these 2-diethylaminoethyl esters (I*b*–V*b*) were obtained only as oils. Therefore, they were converted into crystalline hydrochloride salts by treating the free esters with hydrogen chloride gas. The hydrochloride salts were characterized by satisfactory elemental analyses and IR and NMR spectroscopy.

Table I—2-Diethylamino-*cis*- and -*trans*-methylcyclohexanecarboxylates



Methyl Group Position	Relative Configuration of the Substituents	Compound
2	*cis*-	I*a*, R = H; I*b*, R = $CH_2CH_2N(C_2H_5)_2$
2	*trans*-	II*a*, R = H; II*b*, R = $CH_2CH_2N(C_2H_5)_2$
3	*cis*-	III*a*, R = H; III*b*, R = $CH_2CH_2N(C_2H_5)_2$
4	*cis*-	IV*a*, R = H; II*b*, R = $CH_2CH_2N(C_2H_5)_2$
4	*trans*-	V*a*, R = H; V*b*, R = $CH_2CH_2N(C_2H_5)_2$



VI

Table II—Anticancer Activity of Compounds I*b*–V*b* and VI

Compd.	Test System[a]	Dose, mg./kg.	Survivors ( ) of ( )		Stage Index
I*b*	SA	125	6	6	0.66
	CA	100	10	10	1.26
	LE	100	6	6	0.94
II*b*	SA	100	6	6	0.93
	CA	200	10	10	0.55
	LE	80	6	6	0.87
	HI	20	6	6	0.50
	HI	20	5	6	0.25
III*b*	SA	250	6	6	0.71
	CA	200	8	10	0.93
	LE	200	6	6	0.88
IV*b*	SA	250	6	6	1.10
	CA	200	10	10	0.53
	CA	200	9	10	0.71
	LE	200	6	6	0.93
V*b*	SA	250	6	6	0.67
	CA	200	10	10	0.83
	LE	200	6	6	0.93
VI	SA	250	6	6	0.96
	CA	200	10	10	1.00
	LE	200	6	6	0.88

[a] SA = sarcoma-180; CA = adenocarcinoma-755; LE = L-1210 lymphoid leukemia; and HI = HS1 human sarcoma (rat, egg).

ANTICANCER ACTIVITY

All the 2-diethylaminoethyl-methylcyclohexanecarboxylates described in this paper were evaluated in the routine mouse tumor

Table III—2-Diethylaminoethyl-methylcyclohexanecarboxylates

Compd.[a]	B.p. (mm. Hg.)	Ref. Index, n_D^{25}	Yield, %	Hydrochloride salt, m.p.	Anal., % Calcd. C	Calcd. H	Found C	Found H
I*b*	116–118° (1.00)	1.4601	70	120–120.5°	60.52	10.16	60.62	10.03
II*b*	114–115° (2.4–2.6)	1.4542	85	117–117.5°	60.52	10.16	60.30	9.96
III*b*	114–114.5° (1.5–1.7)	1.4542	81	100–101°	60.52	10.16	60.59	10.21
IV*b*	115–116° (1.8–1.9)	1.4551	46	123.5–124.5°	60.52	10.16	60.61	10.26
V*b*	118–119° (2.2–2.4)	1.4533	73	154–155°	60.52	10.16	60.76	10.16

[a] All the compounds I*b*–V*b* had empirical formula $C_{14}H_{28}ClNO_2$.

screening of the Cancer Chemotherapy National Service Center, Bethesda, Md. (13). The results are mentioned in Table II. None of the compounds prepared in this investigation showed confirmed anticancer activity. Hence, no correlation could be drawn between an equatorial–equatorial or an axial–equatorial arrangement of the methyl and the diethylaminoethoxycarbonyl groups on the cyclohexane ring of a compound and the anticancer activity of that compound.

EXPERIMENTAL

The melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. The IR spectra were recorded on a Beckman IR-8 spectrophotometer. The NMR spectra were obtained with a Varian A-60 spectrometer.

Preparation of Methylcyclohexanecarboxylic Acids I*a*–V*a*—*cis*-2-Methylcyclohexanecarboxylic acid (I*a*) was prepared by catalytic hydrogenation of *o*-toluic acid by the procedure of MacBeth *et al.* (9) and Cope *et al.* (8). It had b.p. 130–130.5° (10 mm.), n_D^{23} 1.4631 [lit. (9) b.p. 119° (11 mm.), n_D^{20} 1.4644].

trans-2-Methylcyclohexanecarboxylic acid (II*a*) was prepared by heating crotonic acid with 1,3-butadiene in a pressure vessel by the procedure of Diels and Alder (10). It had m.p. 51–52.5° [lit. (14) m.p. 52°].

cis-3-Methylcyclohexanecarboxylic acid (III*a*) was prepared by the catalytic hydrogenation of *m*-toluic acid by the procedure of Darling *et al.* (15). It had b.p. 98–99° (1.3–1.8 mm.), n_D^{25} 1.4561 [lit. (15) b.p. 98–99° (1.2 mm.), n_D^{20} 1.4570].

cis-4-Methylcyclohexanecarboxylic acid (IV*a*) was prepared by the hydrogenation of *p*-toluic acid by the procedure of Delephine and Badoche (11). It had b.p. 96.5–98° (1.25–1.70 mm.), n_D^{25} 1.4581 [lit. (11) b.p. 128–130° (13 mm.), n_D^{16} 1.4605].

trans-4-Methylcyclohexanecarboxylic acid (V*a*) was prepared by heating IV*a* in the presence of hydrogen chloride gas by the procedure of Delephine and Badoche (11). It had m.p. 108–110° [lit. (11) m.p. 111°].

Preparation of 2-Diethylaminoethyl Esters—*2-Diethylaminoethyl-cis-2-methylcyclohexanecarboxylate* (*I*b)—To a solution of *o*-toluoyl chloride (23.8 g., 0.153 mole) in anhydrous ether (50 ml.) was added in small portions, with shaking and cooling, freshly distilled 2-diethylaminoethanol (0.380 mole). The reaction mixture was allowed to stand at room temperature overnight. A saturated solution of sodium carbonate (100 ml.) and ether (50 ml.) was added to the solution. The ether layer was separated and the aqueous layer extracted with ether twice. The combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated to yield an oil. Fractional distillation of the oil afforded 31.0 g. (75%) of 2-diethylaminoethyl-*o*-toluate (VI) as a colorless oil, b.p. 133–135.5° (1.9–2.1 mm.), n_D^{25} 1.5021. A solution of VI (9.8 g., 0.042 mole) in glacial acetic acid (60 ml.) was mixed with platinum oxide (0.31 g.) and hydrogenated at 60 p.s.i. pressure of hydrogen gas. The temperature was maintained at 90° for 5 hr. and at room temperature for 16 hr. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure (100 mm.) to get rid of all the acetic acid. Fractional distillation of the residual oil afforded 7.0 g. (70%) of 2-diethylaminoethyl-*cis*-2-methylcyclohexanecarboxylate (I*b*) as a colorless oil, b.p. 116–118° (1 mm.), n_D^{22} 1.4601.

For the sake of characterization, a small amount of I*b* was converted into its crystalline hydrochloride salt by adding dropwise an ethereal solution of hydrogen chloride to an ethereal solution of I*b* until the solution became acidic. The precipitated hydrochloride salt was filtered and recrystallized from absolute ethanol–ether. It had m.p. 120–120.5°.

General Procedure for the Preparation of Esters II*b*–V*b*—Esterification of the methylcyclohexanecarboxylates II*a*–V*a* was carried out by the method of Rabjohn (12). This procedure involved heating the potassium salt of the carboxylic acid with 2-chlorotriethylamine hydrochloride in toluene during 25–30 hr. Filtration (to remove the precipitated KCl), removal of toluene by evaporation under reduced pressure, and fractional distillation afforded the esters II*b*–V*b* in 70–90% yields. The boiling points, refractive indexes, and yields of the esters II*b*–V*b* are given in Table III. All the esters were converted into crystalline hydrochloride salts by bubbling anhydrous hydrogen chloride gas into an ethereal solution of the ester until the solution turned acidic. The precipitated hydrochloride salts were filtered and recrystallized from absolute ethanol–ether. The melting points and analyses are also given in Table III.

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