4-ARYL-3-(DIMETHYLAMINOMETHYL)THIACYCLOHEXAN-4-OLS INCLUDING THE THIA ANALOGUE OF TRAMADOL; SYNTHESIS AND ANALGETIC ACTIVITY

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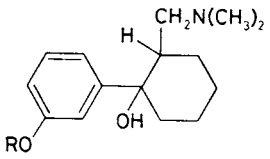
Mannich reaction of thiacyclohexan-4-one with dimethylamine and paraformaldehyde afforded 3-(dimethylaminomethyl)thiacyclohexan-4-one (*XIV*) which was subjected to reactions with a series of arylmagnesium bromides. The products were mixtures of *trans*- and *cis*-amino alcohols *III*—*XII* from which the predominating *trans*-components were mostly obtained by crystallization of hydrochlorides or chromatography of bases. The tramadol (*I*) analogue, *i.e.* the 3-methoxy compound *V*, was prepared in the form of both racemates and their relative configuration was confirmed by the IR spectra. Compound *V* was demethylated to the 3-hydroxyphenyl analogue *XIII*, transformed to the bis-onium salt *XVI*, partially N-demethylated to the N-monodemethyl analogue *XVII*, and oxidized to the sulfoxide *XX* and to the sulfone N-oxide *XXI*. Some of the amino alcohols (*III*—*V*, *VIII*, *IX*, *XIII*) showed clear analgetic activity in the writhing syndrome inhibition test in mice; the 3-methoxy and 3-hydroxy compounds (*V* and *XIII*) were the most active ones, the latter being slightly more active than tramadol (*I*).

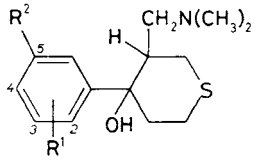
Structural modifications of the morphine molecule, especially the simplifications, were investigated in enormous extent with the purposes to find synthetically easily accessible compounds and to remove, or at least diminish, the addiction liability which is connected with the analgetic effects of morphine[1]. As one of the structural types, variously substituted 1-aryl-2-(tert.aminomethyl)cyclohexanes were studied by several reserach groups[2-5]; promising analgetically active substances were found within the series of 1-aryl-2-(dimethylaminomethyl)cyclohexanols[6,7]. The practical result was *trans*-1-(3-methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol (*I*) (refs[8,9]) whose rather strong analgetic activity and low addiction liability were described in pharmacological papers[10,11]. Under the generic name tramadol (ref.[12]), the substance found therapeutic use and clinical reports[13-15] characterized it as being effective in providing good relief of pain in various medical conditions. Having made interesting and useful experiences with the thia analogues (isosteres) of pharmacodynamically active agents (substitution of methylene group by the sulfur atom), we decided to apply this principle to the molecule of tramadol (*I*) and designed, synthesized and tested a series of 4-aryl-3-(dimethylaminomethyl)thiacyclohexan-4-ols. The description of our experimental work is the object of the present communication.



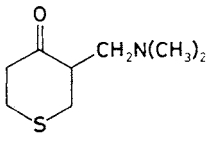
I, R = CH_3
II, R = H

In the first line, the synthesis of amino alcohols *III*–*XII* was carried out. The starting thiacyclohexan-4-one (tetrahydro-4*H*-thiopyran-4-one) was obtained in three steps either from methyl acrylate or ethyl acrylate. Addition of hydrogen sulfide gave dimethyl 4-thiaheptanedioate[16,17], and diethyl 4-thiaheptanedioate[18], respectively. Dieckmann cyclizations with sodium methoxide in ether resulted in methyl 4-oxo-1-thiacyclohexane-3-carboxylate[19] and ethyl 4-oxo-1-thiacyclohexane-3-carboxylate[20,21] (this was not purified) which were hydrolyzed and decarboxylated by heating with 10–15% sulfuric acid[18–20,22]. Thiacyclohexan-4-one was subjected to Mannich reaction with dimethylamine hydrochloride and paraformaldehyde in boiling water. The hydrochloride of the Mannich base *XIV* was obtained in crystalline form. The base *XIV*, released with sodium hydroxide, was oily and not homogeneous. Chromatography of a sample of one batch of this base on silica gel afforded 20% of a less polar crystalline substance having – according to the analysis and the mass spectrum the elemental composition $C_{14}H_{23}NO_2S_2$. The compound contains *per* one dimethylamine residue two thiacyclohexanone and two formaldehyde fragments; structure *XV* is proposed for this product. This structure, however, does not explain the presence of a band at 3 380 cm^{-1} in the IR spectrum (in addition to the expected ketone band at 1 710 cm^{-1}), which indicates a hydroxyl group; it must, therefore, be considered a tentative one.

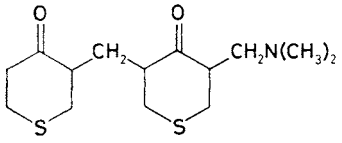
The amino alcohols *III*–*XII* were prepared by the general method consisting in reactions of the Mannich base *XIV* with Grignard reagents, obtained from bromobenzene, 2-, 3- and 4-bromoanisoles, 2-, 3- and 4-bromochlorobenzenes, 3- and 4--bromobenzotrifluorides, and 3,5-bis(trifluoromethyl)bromobenzene. 3,5-Bis(trifluoromethyl)bromobenzene was prepared from 3,5-bis(trifluoromethyl)aniline by diazotization and the Sandmeyer reaction; its formation by direct bromination of 1,3-bis(trifluoromethyl)benzene was mentioned in the literature[23]. The Grignard reactions were carried out in ether, tetrahydrofuran or in mixtures of both solvents. The reaction mixtures were decomposed with tartaric acid solutions and the released bases were either directly transformed to the hydrochlorides or first chromatographed on silica gel. The crude bases were mixtures of *trans*- and *cis*-racemates in which the predominance of the *trans* (*i.e.* 3-H,4-OH-*trans*) racemates was expected (in analogy with the tramadol series[8]). It was confirmed in the case of the 3-methoxyphenyl compound *V*, where the isomers were separated by chromatography on silica



III, $R^1 = R^2 = H$
IV, $R^1 = 2\text{-}OCH_3$; $R^2 = H$
V, $R^1 = 3\text{-}OCH_3$; $R^2 = H$
VI, $R^1 = 4\text{-}OCH_3$; $R^2 = H$
VII, $R^1 = 2\text{-}Cl$; $R^2 = H$
VIII, $R^1 = 3\text{-}Cl$; $R^2 = H$
IX, $R^1 = 4\text{-}Cl$; $R^2 = H$
X, $R^1 = 3\text{-}CF_3$; $R^2 = H$
XI, $R^1 = 4\text{-}CF_3$; $R^2 = H$
XII, $R^1 = 3\text{-}CF_3$; $R^2 = CF_3$
XIII, $R^1 = OH$; $R^2 = H$



XIV

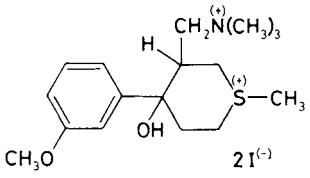


XV

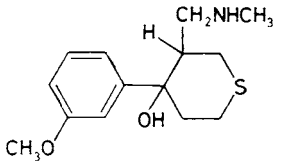
gel. The major and less polar base A and the minor more polar base B were obtained in the ratio 5 : 1. Their configuration were confirmed by the IR spectra: the base A in a high dilution in tetrachloromethane showed the band at 3 160 cm^{-1} corresponding to the hydroxyl group being completely in hydrogen bond with the amino nitrogen atom; on the other hand, the base B under similar conditions exhibited the band of the free hydroxyl group at 3 600 cm^{-1}. The hydrochlorides of the amino alcohols *III*–*XII*, which were crystallized until reaching the constant melting point, are considered practically pure *trans*-compounds. The spectra were recorded either with the hydrochlorides or with the bases (crystalline or oily). Amino alcohols *III*–*XII* are assembled in Table I with the usual experimental data. The synthesis of compound *V* is described with details in the Experimental as an example.

With regard to the fact that in the tramadol series the 3-hydroxyphenyl analogue *II* is the analgetically most active substance[7], the demethylation of our compound *trans-V* was carried out with boron tribromide in dichloromethane at room temperature. The amphoteric oily base *XIII* gave the hydrochloride and the structure was corroborated by spectra. Treatment of the *trans-V* base with excessive methyl iodide in methanol gave the expected bis-onium salt *XVI*. In order to synthesize the N-monodemethyl analogue *XVII* of compound *V* (the potential metabolite), the base *trans-V* was treated with ethyl chloroformate in benzene at room temperature. In a high yield there crystallized the hydrochloride of a base which was identified by analysis and spectra as the mixed carbonate *XVIII*. The base, released with aqueous sodium

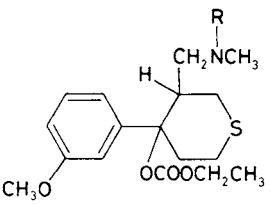
carbonate, was treated again with ethyl chloroformate in boiling benzene. The neutral oily product, obtained in an almost quantitative yield, was evidently the desired carbamate carbonate *XIX* (not characterized) because its hydrolysis with ethanolic potassium hydroxide afforded the secondary amine *XVII* which was



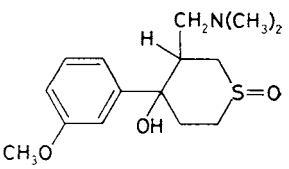
XVI



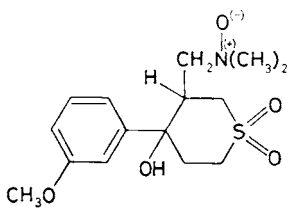
XVII



XVIII, R = CH_3
XIX, R = $COOC_2H_5$



XX



XXI

transformed to the hydrochloride and whose identity was confirmed especially by the mass and IR spectra. Oxidation of compound *trans-V* with a slight excess of hydrogen peroxide in acetic acid at room temperature gave an amorphous base which was transformed to the hydrochloride and identified as the sulfoxide *XX* (the band at 1 030 cm^{-1} in the IR spectrum and the polarographic reduction). A similar oxidation with a large excess of hydrogen peroxide and longer standing at room temperature led to the attack not only at the atom of sulfur but simultaneously at the nitrogen atom and the product (high-melting base) was identified as the sulfone N-oxide *XXI* (N—O band in the IR spectrum at 924 cm^{-1} and the sulfone bands at 1 125 and 1 287 cm^{-1}).

TABLE I

4-Aryl-3-(dimethylaminomethyl)thiacyclohexan-4-ols and their hydrochlorides

Compound (yield %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found				
			% C	% H	% Cl	% N	% S
III-HCl	243–246[a]	$C_{14}H_{22}ClNOS$	58·41	7·72	12·31	4·87	11·14
(58)	(ethanol–ether)	(287·9)	58·34	7·80	12·36	4·66	11·10
IV-HCl[b]	200–203[c]	$C_{15}H_{24}ClNO_2S$	55·11	7·72	10·84	4·29	9·81
(66)	(ethanol–ether)	+ 0·5 H_2O	55·57	7·87	11·04	4·36	9·80
		(326·9)					
V-HCl[d,e]	203–204	$C_{15}H_{24}ClNO_2S$	56·67	7·62	11·15	4·41	10·08
(76)	(ethanol–ether)	(317·9)	56·71	7·61	11·40	4·36	10·20
VI-HCl	204–207[f]	$C_{15}H_{24}ClNO_2S$	56·67	7·62	11·15	4·41	10·08
(40)	(ethanol–ether)	(317·9)	56·52	7·78	11·03	4·25	10·00
VII-HCl	256–258[g]	$C_{14}H_{21}Cl_2NOS$	52·16	6·58	22·00	4·35	9·95
(34)	(ethanol–ether)	(322·3)	51·98	6·65	22·28	4·25	9·80
VIII-HCl	251–254[h]	$C_{14}H_{21}Cl_2NOS$	52·16	6·58	22·00	4·35	9·95
(43)	(ethanol)	(322·3)	52·30	6·68	21·91	4·29	10·06
IX	98–100[i]	$C_{14}H_{20}ClNOS$	58·82	7·07	12·40	4·90	11·22
(43)	(acetone–heptane)	(285·9)	58·98	7·13	12·30	4·74	11·45
IX-HCl	209–211	$C_{14}H_{21}Cl_2NOS$	52·17	6·58	22·00	4·35	9·95
	(ethanol–ether)	(322·3)	52·35	6·72	21·44	4·32	10·25
X-HCl[b]	209–211·5[j]	$C_{15}H_{21}ClF_3NOS$	49·37	6·09	9·72	3·84	8·79
(61)	(ethanol–ether)	+ 0·5 H_2O	49·27	5·87	10·04	3·84	8·97
		(364·9)					
XI	87–88[k]	$C_{15}H_{20}F_3NOS$	56·40	6·32	17·84[l]	4·39	10·04
(43)	(acetone–heptane)	(319·4)	56·58	6·44	18·09	4·34	10·10
XI-HCl	256–259	$C_{15}H_{21}ClF_3NOS$[m]	50·62	5·96	9·96	3·94	9·01
	(ethanol)	(355·9)	50·56	6·02	10·09	3·97	9·23
XII-HCl	239–241·5[n]	$C_{16}H_{20}ClF_6NOS$[o]	45·33	4·77	8·36	3·31	7·56
(33)	(ethanol–ether)	(423·9)	45·27	5·21	8·29	3·16	7·59

[a] IR spectrum: 710, 772 (5 adjacent Ar—H), 2 450, 2 495, 2 535 (NH^+), 3 280 cm^{-1} (OH), [b] Hemihydrate. [c] Mass spectrum, *m/z* (composition and %): 281 (M^+ corresponding to $C_{15}H_{23}NO_2S$, 1%), 163 ($C_{10}H_{11}O_2$, 1), 135 ($C_8H_7O_2$, 2·5), 86 ($C_5H_{12}N$, 4), 84 ($C_5H_{10}N$, 2·5), 77 (2), 58 ($CH_2{=}\overset{(+)}{N}(CH_3)_2$, 100); IR spectrum: 760 (4 adjacent Ar—H), 1 165 (tert. C—OH), 1 224 ($ArOCH_3$), 1 480, 1 580, 1 595, 3 010 (Ar), 2 460, 2 550 (NH^+), 3 260, infl. 3 460 cm^{-1} (OH, H_2O); the oily base was released with NH_4OH, isolated by extraction with ether and its ^1H NMR spectrum was recorded: δ 7·80 (dd, J = 8·5; 2·0 Hz, 1 H, 6-H in methoxyphenyl), 6·80–7·30 (m, 3 H, remaining ArH), 3·85 (s, 3 H, OCH_3), 2·05 (s, 6 H, $N(CH_3)_2$), 1·60–3·70 (m, 4 CH_2, CH and OH). [d] Considered to be the homogeneous *trans*-isomer. [e] See Experimental. [f] IR spec-

The compounds prepared were pharmacologically tested mostly in the form of hydrochlorides; the doses given (in mg/kg) were calculated *per* bases. Some of the data are assembled in Table II. Acute toxicities in mice on intravenous administration are given there (LD_{50}). The analgetic activity was evaluated in the test of inhibition of the writhing syndrome in mice[24]; the nociceptive reaction was elicited by intraperitoneal injection of 3% acetic acid. The data in Table II show that optimum substitution in the aromatic ring is represented by 3-methoxy (*V*, VÚFB-15 581) and 3-hydroxy (*XIII*, VÚFB-15 585) which corresponds to the tramadol (*I*, included in Table II as a standard) series[7], as well as to the morphine series[1]. 3-Hydroxy compounds (*II* and *XIII*) are the most active ones. Methoxy group in 2- or 4-position of the benzene ring influences the activity less favourably. Their substitution with the atom of chlorine or trifluoromethyl leads to further decrease of activity (the 3-chloro compound was the only one showing clear activity) or to inactivation. The same is true about all structural changes leading to more polar compounds (bis--onium salt *XVI*, secondary amine *XVII*, sulfoxide *XX* and sulfone N-oxide *XXI*). The compounds were also tested for analgetic activity by a similar method but using the rat as the experimental animal; the data obtained in this way were less reliable and the test in rats seems to be useful for qualitative characterization only.

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trum: 830 (2 adjacent Ar—H), 1 030, 1 070, 1 250 ($ArOCH_3$), 1 175 (tert. C—OH), 1 510, 1 605, 3 000 (Ar), 2 460, 2 670 (NH^+), 3 340 cm^{-1} (OH); ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·38 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of methoxyphenyl), 6·85 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of methoxyphenyl), 3·71 (s, 3 H, OCH_3), 2·45 (bs, 6 H, $N(CH_3)_2$), 1·80—3·30 (m, 4 CH_2, CH and OH). [g] Mass spectrum, *m/z* (composition): 285 (M^+ corresponding to $C_{14}H_{20}ClNOS$), 250 ($C_{14}H_{20}NOS$), 139 (C_7H_4ClO), 86, 84, 58; IR spectrum: 775 (4 adjacent Ar—H), 1 030, 1 088 (tert. C—OH), 1 480, 1 560, 1 585, 3 000, 3 010, 3 050 (Ar), 2 465, 2 515, 2 590 (NH^+), 3 265 cm^{-1} (OH). [h] IR spectrum: 795, 810, 895 (3 adjacent and solitary Ar—H), 1 080 (tert. C—OH), 1 565, 1 594 (Ar), 2 470, 2 510, 2 570 (NH^+), 3 275 cm^{-1} (OH); ^1H NMR spectrum (^2H_2O): δ 7·20 to 7·60 (m, 4 H, ArH), 2·58 (s, 6 H, $N^{(+)}(CH_3)_2$), 1·70—3·20 (m, 4 CH_2, CH and OH). [i] IR spectrum: 805, 823 (2 adjacent Ar—H), 1 092 (tert. C—OH), 1 591, 3 020 (Ar), 2 780, 2 820 (N—CH_3), 3 360 cm^{-1} (OH); ^1H NMR spectrum: δ 7·48 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of chlorophenyl), 7·30 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of chlorophenyl), 6·40 (bs, 1 H, OH), 1·70—3·40 (m, 9 H, 4 CH_2 and CH), 2·06 (s, 6 H, $N(CH_3)_2$). [j] Mass spectrum, *m/z* (composition): 319 (M^+ corresponding to $C_{15}H_{20}F_3NOS$), 201 ($C_{10}H_8F_3O$), 173 ($C_8H_4F_3O$), 145 ($C_8H_4F_3$), 86 ($C_5H_{12}N$), 84 ($C_5H_{10}N$), 58 (C_3H_8N); IR spectrum: 710, 800, 820 (Ar—H), 1 100 (tert. C—OH), 1 135, 1 165, 1 180, 1 325 ($ArCF_3$), 1 480, 3 020 (Ar), 2 465, 2 515, 2 590 (NH^+), 3 240 cm^{-1} (OH). [k] IR spectrum: 780, 805 (2 adjacent Ar—H), 1 070, 1 088 (tert. C—OH), 1 115, 1 120, 1 160, 1 167, 1 325 ($ArCF_3$), 1 615, 3 000, 3 050, 3 075 (Ar), infl. 3 170 cm^{-1} (OH); ^1H NMR spectrum: δ 7·55 (s, 4 H, ArH), 1·95 (s, 6 H, $N(CH_3)_2$), 1·70—3·80 (m, 4 CH_2, CH and OH). [l] Fluorine content. [m] Calculated: 16·02% F; found: 16·22% F. [n] Mass spectrum, *m/z*: 387 (M^+ corresponding to $C_{16}H_{19}F_6NOS$), 269, 241, 213, 86, 84, 58; IR spectrum: 845 (solitary Ar—H), 1 050 (tert. C—OH), 1 121, 1 161, 1 172, 1 278 ($ArCF_3$), 2 450, 2 550 (NH^+), 3 240 cm^{-1} (OH); ^1H NMR spectrum ($C^2H_3O^2H$): δ 7·70—8·30 (m, 3 H, ArH), 2·65 (s, 6 H, $N(CH_3)_2$), 2·00—3·80 (m, 4 CH_2, CH and OH). [o] Calculated: 26·89% F; found: 26·92% F.

The most active 3-hydroxy compound VÚFB-15 585 (*XIII*-HCl) was tested more thoroughly and compared with tramadol (*I*-HCl). Two further tests were used for assessing its analgetic activity (for pharmacological methods, *cf.*[10,24]). In the test of D'Amour and Smith in mice the compound was administered subcutaneously and its ED_{50} = 1·6 mg/kg. In this test compound *XIII* is significantly more active than tramadol (*I*) with the ED_{50} between 10 and 20 mg/kg. In the hot plate test in mice both compounds were approximately equally active; the oral dose prolonging the latency of the nociceptive reaction by 25%, D_{25} = 25 mg/kg. Both compounds differ in the influencing the locomotor and total activity of mice and rats. In the photo-cell method of Dews compound *XIII* in the oral dose of 10 mg/kg had not influence on the locomotor activity but in the dose of 50 mg/kg it significantly stimulated the activity (tramadol in oral doses up to 100 mg/kg significantly decreased the activity). In the test evaluating the total activity of rats using the Varimex apparatus, compound *XIII* in the subcutaneous dose of 5 mg/kg significantly stimulated the activity; higher doses acted as depressant. Tramadol in the dose of 10 mg/kg *s.c.* significantly decreased the total activity of male rats.

TABLE II

Acute toxicity and analgetic activity of 4-Aryl-3-(dimethylaminomethyl)thiacyclohexan-4-ols and derivatives in mice

Compound	LD_{50} *i.v.*[a]	D *i.v.*[a]	Analgetic Activity ED_{50} *p.o.*[a]
III-HCl	37·8	7	30·0
IV-HCl	29·8		18·5
V-HCl[b]	49·5	8	14·9
VI-HCl	54·0		>50
VII-HCl	44·0	8	>50
VIII-HCl	47·9		17·0
IX-HCl	53·7		c. 50
X-HCl	64·7	8	>100[c]
XI-HCl	60·7	10	>50
XII-HCl	127·0	15	>50
XIII-HCl[d]	47·4[e]		6·2
XVI	75	15	
XVII-HCl	58·1		>50
XX-HCl	191	40	>50
XXI	1 000	200	>50
I-HCl[f]	53·1[g]		7·6

[a] All doses in mg/kg. [b] Compound VÚFB-15 581. [c] Lower doses (25 and 50 mg/kg *p.o.*) brought about mild prolongation of latency of the nociceptive reaction. [d] Compound VÚFB-15 585. [e] Oral administration, LD_{50} = 378 mg/kg. [f] Tramadol. [g] Oral administration, LD_{50} = = 237 mg/kg.

A part of the compounds was subjected to a general pharmacological screening. The screened doses (D, *i.v.*) are given in Table II. Compouns *III*, *V*, *VII* and *X*–*XII* in doses D brought about brief and deep drops of the blood pressure in normotensive rats. Compounds *XVI*, *XX* and *XXI* prolonged by 100–300% the pressor response to adrenaline in anaesthetized rats. Compounds *III*, *V*, *X* and *XII* in concentrations of 50 μg/ml showed positive effect on the heart inotropy (increase of inotropy of the isolated rabbit heart atrium by 25%). Some compounds exhibited antitussive action in rats (the oral doses given reduced approximately to 50% the coughing activity elicited by the aerosol of citric acid solution in comparison with the control): *V*, 40 (to 59%); *VII*, 40 (to 49%); *X*, 40 (to 40%); *XII*, 75 (to 55%); *XX*, 200 (to 59%). Antireserpine effect towards hypothermia in mice was found with the following compounds (intraperitoneal ED given): *V*, 8; *VII*, 8; *X*, 4; *XI*, 10 (only indication of activity); *XX*, 40; *XXI*, 200. Antireserpine action in the test of ptosis in mice (intraperitoneal ED given): *X*, 8; *XXI*, 200. Compounds *XI* and *XII* in concentrations of 10 μg/ml showed spasmolytic activity on the isolated rat duodenum against barium chloride contractions; compound *XI* in concentrations of 1–10 μg/ml was similarly active towards acetylcholine contractions. Compound *XI* in the concentration of 1% had local anaesthetic effect in guinea-pigs (infiltration anaesthesia).

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with the spectrometers MCH 1320 and/or Varian MAT 44 S. The homogeneity of the compounds and the composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

3-(Dimethylaminomethyl)thiacyclohexan-4-one (*XIV*)

A stirred mixture of 159 g thiacyclohexan-4-one[18–20,22], 26 g paraformaldehyde, 61 g dimethylamine hydrochloride, 80 ml water and 3 ml hydrochloric acid was refluxed for 10 min, cooled, diluted with 400 ml water, and extracted with ether. Evaporation of the extract recovered 59 g of the starting ketone. Evaporation of the aqueous layer gave 168 g (93% *per* conversion) crude *XIV* hydrochloride, m.p. 148–149°C. A sample was crystallized from a mixture of ethanol and ether for analysis, m.p. 156–158°C. IR spectrum: 1 484 (C—H in CH_3, CH_2 and CH_2CO), 1 695 (CO in the ring), 2 490, 2 525, 2 650, 2 670, 2 690 cm^{-1} (NH^+). ^{1}H NMR spectrum ($C^2H_3O^2H$): δ 2·88 (s, 6 H, $N(CH_3)_2$), 2·10–3·70 (m, 4 CH_2 and CH). For $C_8H_{16}ClNOS$ (209·8) calculated: 45·80% C, 7·70% H, 16·90% Cl, 6·68% N, 15·28% S; found: 45·99% C, 7·79% H, 17·06% Cl, 6·67% N, 15·18% S.

The crude hydrochloride was treated with a solution of NaOH and the base *XIV* was isolated by extraction with ether; 83·9 g (56%) oil. In this form it was used in the Grignard reactions.

A sample of 10·0 g of another batch was chromatographed on a column of 50 g silica gel. Elution with chloroform and chloroform containing 5% methanol gave 2·0 g homogeneous compound which crystallized from a mixture of acetone and heptane, m.p. 159—162°C, for which the structure of 3-(dimethylaminomethyl)-5-(4-oxothiacyclohex-3-ylmethyl)thiacyclohexan-4-one (*XV*) is tentatively proposed. Mass spectrum, *m/z*: 301 (M^+ corresponding to $C_{14}H_{23}NO_2S_2$), 58 ($CH_2{=}\overset{(+)}{N}(CH_3)_2$, 100%). UV spectrum: infl. at 244 nm (log ε 2·88). IR spectrum: 1 710 (CO in the ring), 2 765, 2 780, 2 820 (N—CH_2, N—CH_3), 3 380 cm^{-1}. ^1H NMR spectrum: δ 2·18 (s, $N(CH_3)_2$), 1·50—3·80 (m, CH_2 and CH groups). For $C_{14}H_{23}NO_2S_2$ (301·4) calculated: 55·80% C, 7·69% H, 4·65% N, 21·24% S; found: 56·25% C, 7·81% H, 4·35% N, 21·19% S.

1-Bromo-3,5-bis(trifluoromethyl)benzene

A solution of 50 g 3,5-bis(trifluoromethyl)aniline in a mixture of 77 ml 48% hydrobromic acid and 105 ml water was cooled to 0°C and diazotized under stirring by a slow addition of a solution of 24 g 85% KNO_2 in 110 ml water (temperature maintained at 0°C). The excess of HNO_2 was removed by the addition of urea and the cooled suspension of the diazonium salt was slowly added to a stirred solution of CuBr in 45 ml 48% hydrobromic acid (CuBr was prepared from 20 g KBr, 27·5 g $CuSO_4.5\,H_2O$ and 7·0 g Na_2SO_3) which was heated to 60—70°C. The mixture was stirred for 1·5 h at 90°C and distilled with steam. The distillate (1·5 l) was extracted with ether, the extract was washed with dilute H_2SO_4, 10% NaOH and water, dried, and evaporated. The residue gave by distillation 21·3 g (33%) product boiling at 54°C/2 kPa. For $C_8H_3BrF_6$ (293·0) calculated: 32·79% C, 1·03% H, 27·27% Br, 38·91% F; found: 32·52% C, 1·08% H, 26·80% Br, 38·91% F.

4-(3-Methoxyphenyl)-3-(dimethylaminomethyl)thiacyclohexan-4-ol (*V*)

The reaction of 32 g Mg with 40 g 3-bromoanisole in 200 ml ether was initiated by a grain of iodine and the refluxing mixture was slowly treated under stirring with further 180 g 3-bromoanisole in 550 ml ether. Addition of 100 ml tetrahydrofuran kept the precipitating Grignard reagent in solution and the mixture was refluxed for 1 h. After coling to 0°C, a solution of 102 g *XIV* in 300 ml tetrahydrofuran was added dropwise, the mixture was then stirred without cooling for 1·5 h, and decomposed by a solution of 500 g (+)-tartaric acid in 4 l water. The organic layer was removed and the aqueous layer was washed with ether. It was then made alkaline with a solution of NaOH, the base was extracted with ether, the extract was washed with water, dried, and evaporated; 152 g (92%) mixture of geometrical isomers of *V*. This could be transformed directly by the action of HCl and repeated crystallization to the hydrochloride of the isomer A.

A sample of 12 g of the mixture of bases was chromatographed on a column of 230 g silica gel. Elution with chloroform and chloroform containing 1% methanol gave 10·0 g homogeneous oily base A. It was dissolved in ethanol and the solution was neutralized by a solution of HCl in ether; hydrochloride of the isomer A, m.p. 203—204°C (ethanol–ether). IR spectrum: 706, 785, 875 (3 adjacent and solitary Ar—H), 1 160 (tert. C—OH), 1 216, 1 290 ($ArOCH_3$), 1 475, 1 483, 1 582, 1 610 (Ar), 2 460, 2 500, 2 540, 2 560 (NH^+), 3 295 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3O^2H$): δ 6·70—7·40 (m, 4 H, ArH), 3·80 (s, 3 H, OCH_3), 2·60 (bs, $N(CH_3)_2$), 2·00—3·40 (m, CH_2 groups, CH and OH). The analysis is included in Table I.

The base *V*-A was released from the hydrochloride with a solution of NaOH and was isolated by extraction with ether; it remained oily. UV spectrum: λ_{max} 272·5 nm (log ε 3·41), 279 nm (3·36). IR spectrum (film): 703, 777, 879 (3 adjacent and solitary Ar—H), 1 050, 1 257 ($ArOCH_3$), 1 480, 1 580, 1 600, 1 605 (Ar). 2 785, 2 830 (N—CH_3), 3 160, 3 390 cm^{-1} (O—H...N and OH). In high dilution (5 mg in 10 ml) in CCl_4 OH appears only in the band at 3 160 cm^{-1}, *i.e.* OH

is completely bound in the hydrogen bond. ^{1}H NMR spectrum: δ 6·60—7·30 (m, 4 H, ArH), 3·80 (s, 3 H, OCH_3), 2·05 (s, 6 H, $N(CH_3)_2$), 2·00—3·40 (m, remaining CH_2, CH and OH groups).

The chromatography was continued by elution with chloroform containing 3% methanol; 2·0 g homogeneous base B which crystallized, m.p. 87—89°C (acetone–heptane). Mass spectrum, *m/z* (composition): 281 (M^+ corresponding to $C_{15}H_{23}NO_2S$), 134 ($C_8H_7O_2$), 86 ($C_5H_{12}N$), 84 ($C_5H_{10}N$), 58 (C_3H_8N). UV spectrum: λ_{max} 273·5 nm (log ε 3·33), 280 nm (3·28). IR spectrum: 786, 812, 870 (3 adjacent and solitary Ar—H), 1 079 (cyclic tert. C—OH), 1 040, 1 255 ($ArOCH_3$), 1 480, 1 595 (Ar), 2 775 (N—CH_3), infl. 3 160 cm^{-1} (OH). In high dilution in CCl_4 the OH group appears as the band at 3 600 cm^{-1}. ^{1}H NMR spectrum: δ 6·60—7·40 (m, 4 H, ArH), 5·40 (bs, 1 H, OH), 3·80 (s, 3 H, OCH_3), 2·75 (m, 4 H, CH_2SCH_2), 1·80—2·50 (m) and 2·03 (s) (together 11 H, CH_2—C—$CHCH_2N(CH_3)_2$). For $C_{15}H_{23}NO_2S$ (281·5) calculated: 64·01% C, 8·25% H, 4·98% N, 11·39% S; found: 64·03% C, 8·50% H, 4·98% N, 11·28% S.

4-(3-Hydroxyphenyl)-3-(dimethylaminomethyl)thiacyclohexan-4-ol (*XIII*)

A solution of 8·5 g *V*-A in 75 ml dichloromethane was added dropwise to a stirred solution of 40 g BBr_3 in 90 ml dichloromethane at a maximum temperature of 10°C. The mixture was stirred for 3 h at room temperature, allowed to stand overnight, decomposed with 150 ml water and treated with a solution of Na_2CO_3. The organic layer was separated, dried and evaporated. The residue (7·2 g crude base *XIII*) was dissolved in ethanol and the solution was neutralized with a solution of 1·0 g HCl in 17 ml ether. The precipitated hydrochloride was filtered, washed with ether, and dried *in vacuo*; 5·2 g (57%), m.p. 262—264°C. Analytical sample, m.p. 267—270°C (methanol–ether). Mass spectrum, *m/z* (% and composition): 26 (M^+ corresponding to $C_{14}H_{21}\overset{(+)}{N}O_2S$, 0·2%), 121 (1·5, $C_7H_5O_2$), 86 (3, $C_5H_{12}N$), 84 (2, $C_5H_{10}N$), 58 (100, $CH_2{=}\overset{(+)}{N}(CH_3)_2$), 46 (7). UV spectrum: λ_{max} 276·5 nm (log ε 3·32). IR spectrum: 685, 710, 787, 882 (3 adjacent and solitary Ar—H), 1 073, 1 210 (ArOH), 1 156 (tert. C—OH), 1 475, 1 582, 1 610, 3 020 (Ar), 2 690 (NH^+), 3 220, 3 360 cm^{-1} (OH). ^{1}HNMR spectrum ($C^2H_3SOC^2H_3$): 6·50—7·50 (m, 4 H, ArH), 2·45 (s, 6 H, $\overset{(+)}{N}(CH_3)_2$), 1·80—3·20 (m, CH_2, CH and OH groups). For $C_{14}H_{22}Cl\overset{(+)}{N}O_2S$ (303·9) calculated: 55·33% C, 7·31% H, 11·67% Cl, 4·61% N, 10·55% S; found: 54·60% C, 7·37% H, 11·67% Cl, 4·47% N, 10·50% S.

4-(3-Methoxyphenyl)-3-(dimethylaminomethyl)thiacyclohexan-4-ol Dimethiodide (*XVI*)

A solution of 7·0 g *V*-A in 25 ml methanol and 30 ml nitromethane was treated with 20 g methyl iodide and the mixture was allowed to stand for 6 days. The solvents were evaporated and the residue was crystallized from methanol; 4·8 g (34%) *XVI*, m.p. 225—227°C with decomposition. For $C_{17}H_{29}I_2NO_2S$ (565·3) calculated: 36·12% C, 5·18% H, 44·89% I, 2·48% N, 5·67% S; found: 35·69% C, 5·06% H, 45·05% I, 3·01% N, 5·95% S.

4-(Ethoxycarbonyloxy)-4-(3-methoxyphenyl)-3-(dimethylaminomethyl)thiacyclohexane (*XVIII*)

A stirred solution of 10·0 g *V*-A in 50 ml benzene was treated dropwise with a solution of 5·8 g ethyl chloroformate in 25 ml benzene. A sample of the precipitated product was filtered off and characterized as *XVIII* hydrochloride, m.p. 184—186°C (ethanol–ether). IR spectrum: 700, 788, 876 (3 adjacent and solitary Ar—H), 1 040, 1 260 ($ArOCH_3$), 1 220, 1 260 (COO), 1 487, 1 604 (Ar), 1 744 (ROCOOR'), 2 450, 2 550 cm^{-1} (NH^+). ^{1}H NMR spectrum (at 60°C): δ

6·80—7·50 (m, 4 H, ArH), 4·20 (q, J = 7·0 Hz, 2 H, OCH_2), 3·85 (s, 3 H, OCH_3), c. 2·60 (bs, 6 H, $N^{(+)}(CH_3)_2$), 2·20—3·60 (m, 4 CH_2 and CH), 1·30 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{18}H_{28}ClNO_4S$ (390·0) calculated: 55·43% C, 7·25% H, 9·09% Cl, 3·59% N, 8·22% S; found: 55·66% C, 7·33% H, 9·40% Cl, 3·67% N, 8·40% S.

The remaining suspension of the product was washed with Na_2CO_3 solution, and the released base *XVIII* was extracted with ether. The extract was washed with water, dried, and evaporated; 12·5 g (theoretical yield) crude oily *XVIII*.

4-(3-Methoxyphenyl)-3-(methylaminomethyl)thiacyclohexan-4-ol (*XVII*)

XVIII (12·9 g) was dissolved in 60 ml benzene and the stirred solution was treated dropwise with a solution of 11·6 g ethyl chloroformate in 25 ml benzene. The mixture was refluxed for 3 h, cooled, washed with dilute hydrochloric acid and $NaHCO_3$ solution, dried, and evaporated; 14·5 g (almost theoretical) oily *XIX* which was dissolved in 50 ml ethanol, the stirred solution was treated with 17·0 g KOH, added in portions, and the mixture was refluxed for 8 h. After cooling it was dissolved in water and the product was extracted with ether. The extract was shaken with dilute hydrochloric acid, the aqueous layer was made alkaline with NaOH solution, and the base *XVII* was isolated by extraction with ether; 5·5 g (59%) oil. The base was dissolved in ethanol and the solution was neutralized with 0·75 g HCl in 12·5 ml ether; 4·7 g *XVII* hydrochloride, m.p. 183—184°C (ethanol–ether). Mass spectrum, *m/z* (composition): 267 (M^+ corresponding to $C_{14}H_{21}NO_2S$), 236 ($C_{13}H_{18}NOS$), 206 ($C_{12}H_{14}OS$), 163 ($C_{10}H_{11}O_2$). UV spectrum: λ_{max} 273 nm (log ε 3·32), 279·5 nm (3·28). IR spectrum: 708, 788, 797, 860, 880, 897 (3 adjacent and solitary Ar—H), 1 075 (tert. C—OH), 1 170, 1 225, 1 258, 1 270 ($ArOCH_3$), 1 490, 1 580, 1 600 (Ar), 2 425, 2 465, 2 700, 2 775 (NH_2^+), 3 340 cm^{-1} (NH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·70—7·40 (m, 4 H, ArH), 3·80 (s, 3 H, OCH_3), 2·30 (s, 3 H, $N^{(+)}CH_3$), 1·70—3·40 (m, 4 CH_2, CH and OH). For $C_{14}H_{22}ClNO_2S$ (303·9) calculated: 55·33% C, 7·31% H, 11·67% Cl, 4·61% N, 10·55% S; found: 55·37% C, 7·43% H, 11·63% Cl, 4·61% N, 10·40% S.

4-(3-Methoxyphenyl)-3-(dimethylaminomethyl)thiacyclohexan-4-ol S-Oxide (*XX*)

A cooled solution of 7·0 g *V*-A in 30 ml acetic acid (5°C) was stirred, treated with 2·85 g 30% H_2O_2, and allowed to stand overnight at room temperature. After dilution with water the mixture was made alkaline with NH_4OH and extracted with chloroform. The extract was dried and evaporated, the residue was dissolved in 20 ml ethanol, and the stirred solution was treated with 1·0 g HCl in 17 ml ether; 6·6 g (80%) *XX* hydrochloride, m.p. 214—216°C (ethanol–ether). IR spectrum: 710, 803, 880 (3 adjacent and solitary Ar—H), 1 030, 1 055 (R_2SO, tert. C—OH, $ArOCH_3$), 1 205, 1 250, 1 290 ($ArOCH_3$), 1 485, 1 583, 1 596, 1 610, 3 020 (Ar), 2 480, 2 530, 2 615 (NH^+), 3 220 cm^{-1} (OH). The polarographic reduction in 0·5M-H_2SO_4 (towards a saturated calomel electrode) showed the reduction wave at $E_{1/2}$ −0·90 V corresponding to the sulfoxide. For $C_{15}H_{24}ClNO_3S$ (333·9) calculated: 53·95% C, 7·26% H, 10·62% Cl, 4·20% N, 9·60% S; found: 53·57% C, 7·18% H, 10·77% Cl, 4·13% N, 9·50% S.

4-(3-Methoxyphenyl)-3-(dimethylaminomethyl)thiacyclohexan-4-ol N,S,S-Trioxide (*XXI*)

A solution of 7·0 g *V*-A in 30 ml acetic acid was treated with 15 ml 30% H_2O_2 and allowed to stand for 6 days at room temperature. The mixture was evaporated partly *in vacuo*, the residue was treated with excessive dilute NH_4OH, and allowed to crystallize; 4·6 g (56%), m.p. 172 to 174°C (methanol and 2-propanol). IR spectrum: 710, 786, 820, 855 (3 adjacent and solitary

Ar—H), 924 (N—O), 1 069 (tert. —OH), 1 125, 1 287 (SO_2), 1 185, 1 209 ($ArOCH_3$), 1 582, 1 607 (Ar), 3 560 cm^{-1} (OH). The polarographic reduction in 1M-HCl (towards saturated calomel electrode): reduction wave at $E_{1/2}$ −0·84 V corresponding to the N-oxide. For $C_{15}H_{23}NO_5S$ (329·4) calculated: 54·70% C, 7·04% H, 4·25% N, 9·72% S; found: 54·46% C, 7·17% H, 4·20% N, 9·78% S.

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