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β-Adrenoceptor Blocking Activity of 3-Alkylamino-1-(3-benzo[*b*]thienyloxy)-2-propanols and Closely Related Bicyclic Compounds

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A preliminary pharmacological study of a thiophenic isoster of propranolol and related compounds with a tert. butylamino or homoveratrylamino group instead of the isopropylamino group is described. The synthesis and some pharmacological properties of derivatives in which the benzene ring is replaced by a cyclopentene or cyclohexene ring are also reported. Compounds carrying the tert. butylamino moiety turned out to be similar to propranolol in their pharmacological properties.

β-Blockerwirkung von 3-Alkylamino-1-(3-benzo[b]thienyloxy)-2-propanol und verwandten bizyklischen Verbindungen

Eine vorläufige pharmakologische Prüfung von einem Thiophen-isoster des Propranolols und verwandten Derivaten mit einer tert. Butylamino- oder einer Homoveratrylaminogruppe anstelle der iso-Propylaminogruppe wird beschrieben. Die Herstellung und eine erste pharmakologische Prüfung entsprechender Verbindungen dieses Strukturtypes in denen der Benzolring durch einen Cyclopenten- bzw. Cyclohexenring ersetzt worden ist, werden auch beschrieben. Die tert. Butylverbindungen sind dem Propranolol in ihrer pharmakologischen Wirkung sehr ähnlich.

In previous works[1),2)] we have reported the synthesis of a series of halogenated thienylethanolamine derivatives as well as the strong β-adrenoceptor blocking activity of the thiophenic isoster of dichloroisoproterenol, the first β-blocking agent described.

The planned synthesis of some thienyloxypropanolamine derivatives, thiophenic isosteres of the so called second generation of β-blocking agents, encountered difficulties. These included besides the frequent instability and unavailability of the starting hydroxythiophene derivatives, the problem of simultaneous O-alkylation and C-alkylation of these last compounds.

These difficulties have been overcome by two synthetic approaches which have proved to be useful for the preparation[3)] of a thiophenic analog of propranolol and for that[4),5)] of some thiophenic analogs of metoprolol, toliprolol, bevantolol, tolamolol and „reversed" practolol.

In this paper we wish to report the synthesis of compounds **6** and a preliminary pharmacological study of the β-blocking activity of these compounds and that of the previously described[3)] compounds **1**.

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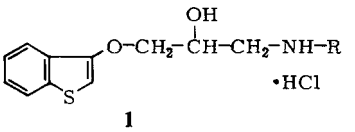

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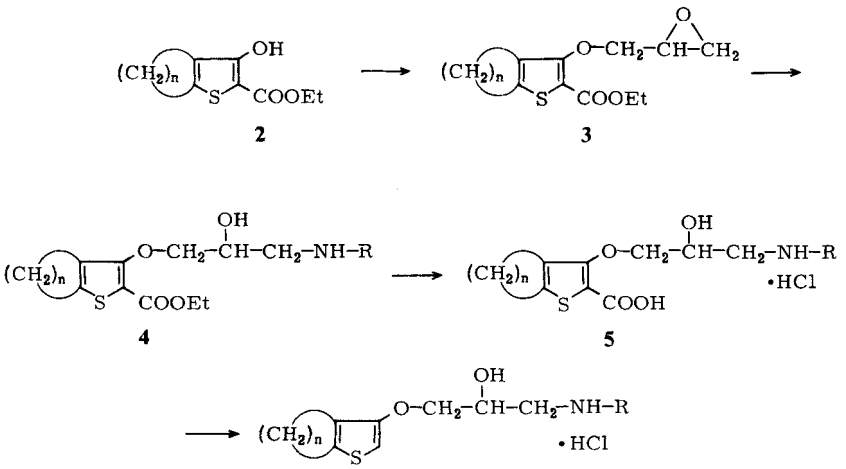
a: R = isopropyl
b: R = tert-butyl
c: R = homoveratryl

Compounds **6**, where n is 3 or 4 and R is isopropyl, tert-butyl or the cardioselectivity confering[6] homoveratryl group, were obtained by one of the above[3] methods as depicted in Scheme 1. Compounds **2a** and **2b**, prepared from 2-ethoxycarbonyl cyclopentanone and 2-ethoxycarbonyl cyclohexanone and ethyl thioglycolate[7], were selectively O-alkylated with epichlorohydrin to give compounds **3a** and **3b**. Treatment at room temperature of the latter with the correponding primary amines in excess (isopropyl or tert-butylamine) or in equimolar solution in isopropanol (homoveratrylamine) yielded compounds **4** isolated either as free bases or/and their hydrochlorides (table 1).

Compounds **4** were hydrolized by heating to reflux their hydroalcoholic solutions containing potassium hydroxide. The isolation of hydrochlorides **5** (table 2) is described in the Experimental Section. An easy decarboxylation of hydrochlorides **5** to compounds **6** (table 3) took place by heating in vacuo 20 or 30 °C above the melting points.



Scheme 1

The results of a preliminary pharmacological testing of the thienyloxypropanolamine derivatives **1** and **6**, are presented in table 4. The blocking activity of the β-adrenoceptors was determined through the degree of antagonism to the cardiovascular actions induced by isoproterenol in anesthetized rats. The tachycardic response to isoproterenol was inhibited in different degrees by all compounds. Compounds **1b**, **6b** and **6e**, all of which contain the tert-butylamino group, appeared to be a little more active than propranolol. These compounds however antagonized in a somewhat different manner the hypotensive response to isoproterenol.

Compounds **1b** and **6e** seem to present a greater capacity for blocking the myocardic than the vascular receptors. This possible cardioselectivity must, however, be quantita-

tively confirmed in further experiments with animals other than rats which are better suited to this tvpe of assay.

All compounds **1** and **6** appeared to be very similar to propranolol in acute toxicity, in decreasing the resting heart rate and in local anesthesic activity in the rats. As in the case of propranolol, these compounds did not show any partial agonistic activity.

Intermediate compounds **4** and **5** having an additional alkoxycarbonyl or carboxy group in position 2 were also tested. As can be seen in table 5, all of them induce a descent of the resting heart rate and arterial pressure. Although most of them inhibit the hypotensive response to isoproterenol, they do not inhibit but enhance in different degrees, the tachycardic response to isoproterenol in the rat.

In contrast to the total absence of partial agonist activity in compounds **1** and **6**, these intermediate compounds possess a certain intrinsic sympathomimetic action which varies from weak to moderate. This effect was dose-dependent from the lowest doses administered and was most marked in compounds bearing the isopropylamino group.

In conclusion, the notable β-blocking activity found in compounds **1a** and **6a** again justifies the pharmacological validity of the isosteric substitution of the benzene ring by the thiophene ring in this field, since both compounds are thiophenic analogues of the well known β-blocking agents propranolol and USVC-6524[8]. The high degree of β-antagonism in the closely related compounds **1b**, **6b** and **6e** is equally worth mentioning. It is also interesting to point out that while dichloroisoproterenol and its thiophenic isoster do possess partial β-agonist activity, the new active compounds don't have any as in the case of propranolol.

We are indebted to *M.J. Lillo* for aid in a part of this work, and to our Department of Analyses and Instrumental Techniques for all the analytical and spectral data.

Experimental Section

MP: a Gallenkamp capillary apparatus, uncorr. *IR*: Perkin-Elmer Model 257 spectrophotometer. *NMR*: Perkin-Elmer R-12. The spectra are consistent with the assigned structures.

Epoxy compounds **3**

2.27 g, (0.24 mol) epichlorohydrin was added dropwise to a solution of 0.1 mol of the corresponding 2-ethoxy carbonyl cyclic ketone and 13.9 g, (0.14 mol) potassium tert. butoxide in 170 ml dry dimethylsulfoxide. The mixture was heated at 100 °C for 1 h and the solvent distilled off at 0.1 mm Hg. The residue was extracted with hot n-hexane, the solvent evaporated from the extract and the oily residue distilled at reduced pressure. Thus, the following compounds are obtained:

2,3-Epoxy-1-[3-(2-ethoxycarbonyl-4H-5,6-dihydrocyclopenta[b]thienyloxy)]propane (**3a**), collected in the fraction with bp 165–175 °C (1 mm Hg). Recrystallized from isopropanol, mp 58–59 °C. Yield 80 %. $C_{13}H_{16}O_4S$ (268.3) Calcd. C 58.2 H 6.01. Found C 58.1 H 5.91.

2,3-Epoxy-1-[3-(2-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thienyloxy)]propane (**3b**), collected in the fraction with bp 160–165 °C (0.5 mm Hg). Recrystallized from isopropanol, mp 50 °C. Yield 84 %. $C_{14}H_{18}O_4S$ (282.3) Calcd. C 59.6 H 6.42 Found C 59.5 H 6.36.

1-[3-(2-Ethoxycarbonyl-4H-5,6-dihydrocyclopenta[b]thienyloxy)]- and 1-[3-(2-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thienyloxy)]-3-alkylamino-2-propanols **4** (table 1)

A) Epoxycompounds **3** and a great excess of isopropylamine or tert. butylamine were left at room temp. for 8 days. The volatile amine excess wass evaporated and the residue dissolved in dry diethylether. From the solution most of the compounds crystallized as the free bases. The mother liquors were treated with ethereal hydrogen chloride to yield the rest of the compounds as their hydrochlorides. When epoxy compounds **3** were treated with smaller excess of the amine in isopropanol the time of reaction was reduced to 4 days.

B) A solution of 0.1 mol of epoxycompounds **3** and 0.1 mol homoveratrylamine in isopropanol was left at room temp. for 4 days, the solvent evaporated and the residue treated as in A.

1-[3-(2-Carboxy-4H-5,6-dihydrocyclopenta[b]thienyloxy)]- and 1-[3-(2-carboxy-4,5,6,7-tetrahydrobenzo[b]thienyloxy)]-3-alkylamino-2-propanols hydrochlorides **5** (table 2)

A solution of 0.1 mol of compound **4** in 580 ml ethanol containing 120 ml of a 20 % aqueous solution of NaOH was heated to reflux for 3 h (24 h in the case of compounds **4c** and **4f** containing the

Table 1: *Compounds* **4**

Compound	n	R	Yield %	M.P. °C	Formula	Calcd. / Found C	H	Analysis N
4a	3	Pr^i	46	67[a]	$C_{16}H_{25}NO_4S$	58.7 59.0	7.63 7.71	4.3 4.4
4a · HCl	3	Pr^i	33	129–130[b]	$C_{16}H_{26}ClNO_4S$	52.8 52.8	7.20 7.31	3.8 3.9
4b	3	Bu^t	70	88–89[a]	$C_{17}H_{27}NO_4S$	59.8 59.7	7.92 8.25	4.1 4.0
4b · HCl	3	Bu^t	11	129–130[b]	$C_{17}H_{28}ClNO_4S$	54.0 54.1	7.42 7.70	3.7 4.0
4c	3	H_v	45	90[a]	$C_{23}H_{31}NO_6S$	61.4 61.7	6.90 7.20	3.1 3.3
4d	4	Pr^i	53	69.5–70.5[a]	$C_{17}H_{27}NO_4S$	59.8 59.8	7.92 8.20	4.1 4.0
4d · HCl	4	Pr^i	27	119–121[b]	$C_{17}H_{28}ClNO_4S$	54.0 54.0	7.42 7.34	3.7 3.8
4e · HCl	4	Bu^t	82	131–133[b]	$C_{18}H_{30}ClNO_4S$	55.4 55.0	7.66 7.83	3.6 3.0
4f	4	H_v	–	Oil	–	–	–	–

a = recrystallized from n-hexane; b = recrystallized from ethanol-ether

homoveratryl group) and the solvent evaporated. The residue was dissolved in water, acidified to pH 4 with dilute hydrochloric acid and the solution evaporated to dryness at 40 °C i. vac. The residue was extracted with absol. ethanol and compounds **5** crystallized from the concentrated ethanolic solution after dilution with anhydrous ether.

Compounds marked with asterisks in table 2, did not resist this isolation method and therefore the alkaline hydrolysis solution was acidified to the isoelectric point with dilute HCl. The precipitated aminoacids were suspended in water and treated with the exact stoichiometric vol. of standard N-HCl. The solution was evaporated to dryness at 40 °C i. vac. and the residue dissolved in absol. ethanol. Crystallization of compounds **5b**, **5c** and **5f** took place when this solution was diluted with dry ether.

Table 2: *Compounds* **5**

Compound	n	R	Yield %	M.P. °C	Formula	Calcd. Found C	H	Analysis N
5a	3	Pr^i	67	142–143 (d)[a]	$C_{14}H_{22}ClNO_4S$	50.1 50.4	6.56 6.81	4.2 4.3
5b*	3	Bu^t	82	167–168 (d)[a]	$C_{15}H_{24}ClNO_4S$	51.5 51.2	6.86 7.13	4.0 4.0
5c*	3	H_v	56	152.5–153.5(d)[a]	$C_{21}H_{28}ClNO_6S$	55.1 55.3	6.12 6.19	3.1 3.2
5d	4	Pr^i	77	140–141 (d)[a]	$C_{15}H_{24}ClNO_4S$	51.5 51.8	6.86 7.05	4.0 4.1
5e	4	Bu^t	71	158–159 (d)[a]	$C_{16}H_{26}ClNO_4S$	52.8 52.7	7.15 7.06	3.8 4.1
5f*	4	H_v	46	111–112 (d)[b]	$C_{22}H_{30}ClNO_6S$	56.0 55.9	6.36 6.61	3.0 3.1

a = recrystallized from ethanol-ether; b = recrystallized from acetonitrile

1-[3-(4H-5,6-Dihydrocyclopenta[b]thienyloxy)]- and
1-[3-(4,5,6,7-tetrahydrobenzo[b]thienyloxy)]-3-alkylamino-2-propanol hydrochlorides **6** (table 3)

Compounds **5** when heated at reduced pressure (0.1 mm Hg) 20 or 30 °C above their melting points for 15 min yielded compounds **6** as oils, which crystallized from ethanol ether.

Pharmacology

Compounds for pharmacological testing were dissolved in 0.05 N-HCl and neutralized with $NaHCO_3$ to pH 7.

Determination of acute toxicity

The approximate DL_{50} in ICR Swiss mice were determined by administering iv und ip the test compounds, using a minimum of at least three doses per compound and five animals per dose. The maximum doses tested were 75 mg/kg iv and 200 mg/k ip.

Direct effects of β-adrenergic blocking activity

Male Wistar rats were anesthetized with Pentobarbital (50 mg/kp ip). Blood pressure was recorded from the carotid artery using a Statham transducer P23 and heart rate was measured by integration of ECG (lead II), recording both parameters in a Grass polygraph. Injections were made into the jugular vein. Standard submaximal doses of isoproterenol were given at 10 min until constant responses were obtained. Test compounds were then administered at the same dose of 5 mg/kg and injections of isoproterenol were repeated another three times at the same intervals of time. Blockade of the tachycardic response to isoproterenol was expressed as the percent mean inhibition of the mean control response. The percent change in resting heart rate after administration of the test compound was also calculated. The rats were heparinized with 1000 I.U./kg/iv and maintained on artificial respiration. Each compound was studied at least on five animals.

Table 3: *Compounds* **6**

Compound	n	R	Yield %	M.P. °C	Formula	Calcd. Found C	H	Analysis N
6a	3	Pr^i	67	149–150	$C_{13}H_{22}ClNO_2S$	53.5 53.5	7.55 7.79	4.8 4.9
6b	3	Bu^t	65	164–165	$C_{14}H_{22}ClNO_2S$	55.0 54.8	7.86 8.17	4.6 4.8
6c	3	H_v	63	111–112	$C_{20}H_{28}ClNO_4S$	58.0 57.9	6.77 7.09	3.4 3.3
6d	4	Pr^i	75	138–139	$C_{14}H_{24}ClNO_2S$	55.0 54.9	7.85 8.05	4.6 4.5
6e	4	Bu^t	77	159–160	$C_{15}H_{26}ClNO_2S$	56.3 56.2	8.14 8.23	4.4 4.3
6f	4	H_v	81	141–142	$C_{21}H_{30}ClNO_4S$	58.9 58.9	7.02 7.29	3.3 3.5

Local Anesthesia

Test compounds (0.1 ml of 0.5–1 % solutions) were intradermically administered to ICR Swiss mice at about 1 cm from the root of the tail. Thirty min later an artery clip was applied to the area of the injection and the response of mice was then evaluated by means of a subjective scale. The percent reduction in the summed scores of control groups (saline-procaine) was calculated. Each solution was tested in five animals.

Partial agonist activity

Tests were carried out on pithed rats according to the technique of *Shipley* and *Tilden*[9]. Lots of three animals were used per compound and the margin of the doses tested was 0.01–1 mg/kg.

Table 4: *Pharmacological testing of compounds* **1** *and* **6**

Compound	Direct effects % Decrease Heart rate	Blood Pressure	% Inhibition of isoproterenol effects Tachycardia[a]	Hypotension[a]	Local anesthesia % inhibition of response[b]	Acute toxicity Aprox. LD_{50} iv	ip
1a	37	21.5	66	77	87	55.0	200
1b	31	15	85	55	100	30.9	125
1c	20	14	31	9	63	33.5	180
6a	34	19	44	52	95	37.2	180
6b	28	8	75.5	78	97	31.8	140
6c	22	5	24	7	68	42.7	180
6d	33	8	54	50.5	90	29.5	130
6e	31	16.5	90	53	100	29.8	100
6f	17	3	20	41	70	35.3	150
Propranolol	33.5	18	73	66	95	23.2	75
Procaine	–	–	–	–	75	–	–

a = Single iv doses of 5 mg/kg. All standard errors of the mean fell within the range of 8–16 % of the mean. b = 0.5 % solution of test compounds. A virtually complete inhibition of response was observed in all cases with 1 % solutions.

Table 5: *Pharmacological testing of compounds* **4** *and* **5**

Compound	Direct effects % Decrease Heart rate	Blood Pressure	% Inhibition of isoproterenol-induced hypotension[a]	Local Anesthesia % inhibition of response[b]	Partial agonist activity	Acute toxicity Approx. LD_{50} iv	ip
4a	28	8	41	75	++	37.5	100
4b	29.5	11	62.5	80	+	65.5	200
4d	22	8	0	68	++	75.0	>200
4e	25	6	0	65	+	31.8	140
5a	22	18	21	100	+	32.5	175
5b	25	13	28	85	±	45.3	150
5c	14.5	14	21	63	±	62.1	200
5d	14	5	13	50	++	>75	>200
5e	20	7	27	50	±	>75	>200
5f	6	18	9	40	±	>75	>200
Propranolol	33.5	18	66	95	0	23.2	75
Procaine	–	–	–	–	75	–	–

a = Single iv doses of 5 mg/kg. All standard errors of the mean fell within the range of 8–16 % of the mean; b = 0.5 % solution of test compounds. A virtually complete inhibition of response was observed in all cases with 1 % solutions.

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Enaminone des Pummerer-Ketons

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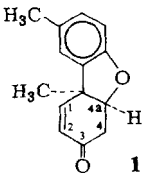
Umsetzung der Titelverbindung **1** bzw. deren 1,2-Dihydroderivat **2** mit Dimethylformamiddimethylacetal ergibt die Enaminoketone **5a** und **6a**. Die durch Aminaustauschreaktionen zugänglichen Derivate **5b–n (6b–n)** bzw. **7a–l (8a–l)** erweisen sich hinsichtlich Reaktivität und Stereochemie als interessant.

Enaminones Derived from Pummerer's Ketone

Pummerer's ketone **(1)** and its 1,2-dihydro derivative **2** react with dimethylformamide dimethylacetal to yield the enaminones **5a** and **6a**. Amine exchange reactions lead to the compounds **5b–n (6b–n)** and **7a–l (8a–l)**, which show interesting reactivities and stereochemical properties.



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**) Herrn Prof. Dr. *K. Jentzsch* mit den besten Wünschen zum 70. Geburtstag gewidmet.

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