diphenylpentanoic acid (25.4 g, 50%). This acid was then heated with $SOCl_2$, followed by cyclohexylamine, and the corresponding amide was reduced as described for the preparation of 1. The crude amine was purified as its nitrate salt and recrystallized from EtOAc (12 g, 33%), mp 156 °C. The aromatic rings were finally reduced as described in the preparation of 4. The maleate of 22 was recrystallized from 2-PrOH: yield 51%; mp 208–210 °C.

***N*,2-Dicyclohexyl-2-(*p*-hydroxyphenyl)ethylamine (23).** To an ice-cold solution (0 °C) of concentrated H_2SO_4 (146 mL) containing α-cyclohexylphenylacetic acid (87.3 g, 0.4 mol) was added dropwise (1 drop every 15 s) concentrated HNO_3 (13 mL). The temperature was kept between 0 and 10 °C, and after 1 h, the mixture was poured into crushed ice. The yellow crystals were filtered, washed several times with H_2O, dried, and recrystallized from cyclohexane–CCl_4 (95:5) to afford 58.1 g (55%) of pure *p*-NO_2 derivative, which was catalytically reduced using PtO_2 (1 g) under 1 kg/cm^2 pressure of H_2. The amine obtained (50 g, 97.5%) was dissolved in H_2O (200 mL) and H_2SO_4 (47.2 mL). The aqueous solution was ice-cooled and diazotized by the dropwise addition of $NaNO_2$ (15.9 g, 0.23 mol) in H_2O (40 mL). The temperature was maintained at 0–5 °C for 1 h, and the solution was then slowly added to a boiling solution with H_2O (200 mL) and H_2SO_4 (22 mL). After 0.25 h, the mixture was cooled, and the brown gum was dissolved in a 10% aqueous Na_2CO_3 solution. The solution was decolorized with charcoal and cooled, and the pH was adjusted to 1 with dilute HCl. The gummy residue was taken up in Et_2O, dried, filtered, and evaporated to afford 27.5 g of crystals after trituation with CCl_4 (100 mL). Recrystallization from CCl_4–$(i\text{-}Pr)_2O$ gave a sample (18.7 g, 38%) that was homogeneous on TLC. A solution of this phenol in MeOH (50 mL) and H_2SO_4 (1 mL) was heated under reflux for 12 h. The mixture was cooled, made alkaline ($NaHCO_3$), and extracted with EtOAc. After evaporation, the methyl ester was purified by SiO_2 column chromatography using graded mixtures of hexane–EtOAc. The viscous ester thus obtained was then benzylated by refluxing for 12 h in EtOH (75 mL) containing 11 g (80 mmol) of K_2CO_3, benzyl chloride (9 mL, 78 mmol), and NaI (1 g). H_2O (800 mL) was added, and the product was extracted with EtOAc (3 × 250 mL) after acidification. The pooled organic phases were dried and evaporated, and the residue was submitted to SiO_2 column chromatography (450 g). Cyclohexane–EtOAc (95:5) eluted the pure ester (19.9 g, 78.4%) as a colorless oil, which slowly crystallized. The ester was saponified (450 mL of a 1:1 mixture of 10% aqueous NaOH and EtOH) for 2 h. The EtOH was removed under reduced pressure, and the aqueous phase was acidified and extracted with EtOAc (3 × 100 mL). This acid (16.3 g, 85.4%) was heated at 70 °C for 3 h in a solution of $SOCl_2$ (3.6 mL) in benzene (40 mL) as described for 1. The resulting acid chloride was reacted then with cyclohexylamine, and the amide was reduced with BH_3/Me_2S. The resulting amine was treated with ethereal HCl, and the HCl salt was debenzylated over Pd/C under 1 kg/cm^2 pressure of H_2. After 4 days, the solution was filtered (Celite) and evaporated to afford crude 23 (11.05 g). An analytical sample (9.6 g, 8.3%) was obtained as heavy crystals from EtOAc–MeOH, mp 244–246 °C.

***N*,2-Dicyclohexyl-2-*p*-tolylethylamine (24).** To sodamide (8.3 g, 220 mmol) in dry benzene (30 mL) was added to *p*-tolylacetonitrile (26.2 g, 200 mmol) during a period of 10 min. The red mixture was stirred and refluxed for 3 h. The heat was then removed, and bromocyclohexane (32.6 g, 200 mmol) in benzene (20 mL) was added at such a rate as to maintain a vigorous reflux. Stirring and refluxing were continued for 12 h. The reaction mixture was cooled, and H_2O (100 mL) was added. The water layer was discarded, the benzene phase was filtered on Celite, and the filtrate was evaporated under vacuum. The oily residue was chromatographed on basic alumina using hexane as eluent to afford pure nitrile (20.7 g, 48%), which slowly crystallized.

The general procedure of Weston[15] was followed in the HBr hydrolysis of the α-cyclohexyl-*p*-tolylacetonitrile to α-cyclohexyl-*p*-tolylacetic acid. The latter was obtained in an 82% yield: mp 142–143 °C; IR ($CHCl_3$) ν 1710 (CO) cm^{-1}. The acid was then transformed into its acid chloride and reacted with cyclohexylamine as described for the synthesis of 1. The resulting amide was finally reduced to 3 using BH_3/Me_2S. The maleate of 3 was recrystallized from CH_3CN and a few drops of MeOH, mp 190–192 °C.

Acknowledgment. The authors are most appreciative of the technical assistance provided by Mr. and Mrs. Schneyder and Mr. Halter and by Synthelabo (LERS) Laboratories (France).

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Inhibitors of Blood Platelet Aggregation. Activity of Some 1*H*-Benz[*de*]isoquinolinecarboximidamides on the in Vivo Blood Platelet Aggregation Induced by Collagen

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A series of 33 1*H*-benz[*de*]isoquinolinecarboximidamides has been prepared and tested in the rat after intraperitoneal (ip) and/or oral (po) administration for their ability to inhibit the in vivo blood platelet aggregation induced by collagen. In this aggregation test, a considerable number of active compounds were found. Fourteen compounds were active when administered ip [0.2 (mmol/kg)/day], five of which also exhibited significant po activity. One compound was toxic after ip administration but was found to be active after po administration without apparent toxicity. It is thought that the solubility of the drug in water is an important factor for the resorption after oral administration and, hence, for its oral activity.

Blood platelets play an important role in hemostasis as well as in thrombosis. Moreover, blood platelets are assumed to play a key role in arterial diseases of various kinds. Drugs that are able to modulate blood platelet functions may find therapeutic use against arterial thrombosis and its consequences, such as myocardial infarction and stroke. A significant number of compounds are claimed as blood platelet aggregation inhibitors; however, in most cases their activity was only assessed in in vitro tests. In vitro tests are very useful to profile compounds which have been proven to be active blood platelet aggregation inhibitors. Some of these tests, e.g., the TXB_2 assay,[1] the malondialdehyde assay,[2] the serotonin uptake inhibition test,[3] the collagen-induced release inhibition test,[4] etc., are widely used and also in our laboratory ap-

(1) H. Sorks, P. Pradella, F. Dray, M. Rigaud, J. Maclouf, and P. A. Bernard, *Prostaglandins* 16, 277 (1978).
(2) J. B. Smith, C. M. Ingerman, and M. J. Silver, *J. Lab. Clin. Med.*, 88, 167 (1976).
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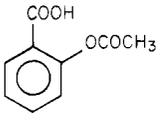
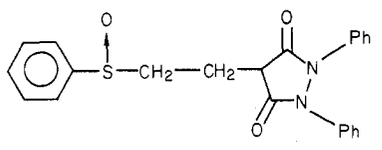
plied routinely. For screening purposes, these tests are hardly used and, in fact, for years the screening test of choice was the Born test,[5] in which the effects of drugs are evaluated in platelet-rich plasma (PRP) after addition of an appropriate aggregation inducer, such as collagen, ADP, arachidonic acid, etc. However, in the past few years it became clear that the Born test, when compared with in vivo data, provides extremely large numbers of false positive and false negative results. The reasons for the discrepancy between the in vitro and in vivo results are discussed in the section "Blood Platelet Aggregation Inhibition". Anyhow, the Born test is an unreliable device for screening potential antiplatelet drugs, and we believe that in vivo tests are much more valuable if it is a question of making predictions about the drug efficacy in man.

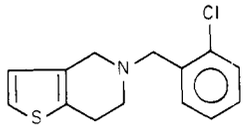
As a result of an at random screening of literally hundreds of compounds in order to establish inhibitory activity in the in vivo blood platelet aggregation test, 2,3-dihydro-1*H*-benz[*de*]isoquinolinecarboximidamide (**26**) proved to exhibit potent activity when administered intraperitoneally (ip) as well as orally (po). This result was of interest not only because compounds of this type are unknown as blood platelet modulating drugs but also because the chemical structure is completely different from drugs such as aspirin (A), sulfinpyrazone (B), ticlopidine



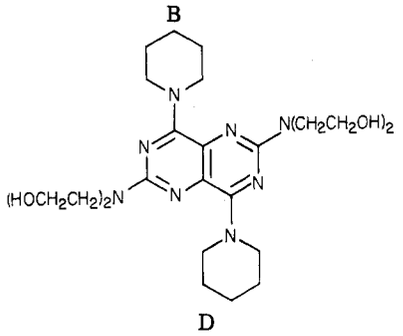
A



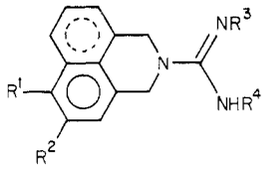
B



C



D



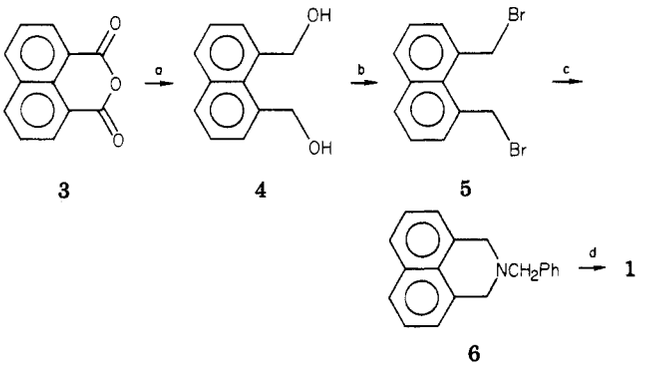
E

(C), or dipyridamole (D), whose efficacies in man have been investigated in clinical trials. For the purpose of screening these type of compounds, we have synthesized a series of 33 substituted 1*H*-benz[*de*]isoquinolinecarboximidamides (E). All compounds synthesized were screened for their ability to inhibit the in vivo blood platelet aggregation induced by collagen. This aggregation test was performed in male Wistar rats. The compounds tested were administered intraperitoneally and/or orally.

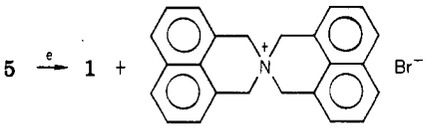
Chemistry. The synthesis of the unsubstituted 2,3-dihydro-1*H*-benz[*de*]isoquinoline (**1**), as described in the literature, proceeds by electrochemical reduction of naphthalimide,[6] acid-catalyzed hydrolysis of *N*-nitroso-

Scheme I[a]

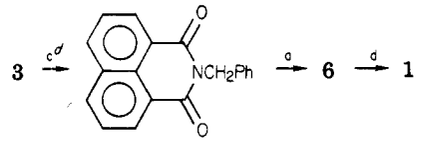
Method I[b]



Method II[c]

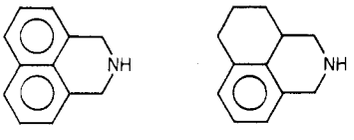


Method III



[a] a = $LiAlH_4$; b = PBr_3; c = $PhCH_2NH_2$; d = Pd/C, H_2; e = NH_3. [b] Reference 8a. [c] Reference 8b. [d] Reference 10.

naphthalimide,[7] or, in very low yield, $LiAlH_4$ reduction of naphthalimide.[7] More convenient preparations were described in the Russian literature by A. I. Tochilkin and collaborators.[8] The synthesis of 2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinoline (**2**) has been performed through a Beckmann or Schmidt reaction of the corresponding tricyclic ketone, followed by a $LiAlH_4$ reduction.[9] Our approach of the synthesis of **1** was based on Tochilkin's method and on an adaptation of it. The saturated compound **2** was prepared through two different and novel pathways.



Synthesis of 1. Synthon **1** and its derivatives were prepared via three different pathways (Scheme I). Method I is essentially the route as proposed by Tochilkin.[8a] Although this route invariably gave **1** (or its congeners) in good yield, we preferred a modification as outlined in

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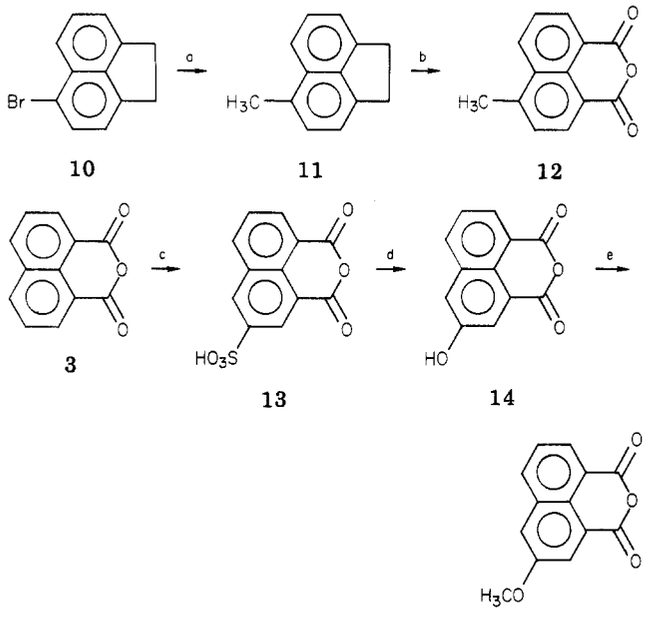
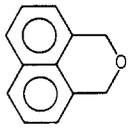
(10) M. El-Garby Younes, *U.A.R. J. Chem.*, **14**, 647 (1971); *Chem. Abstr.*, **79**, 126251g (1973).

Scheme II[a]



[a] a = Mg/CH_3I; b = $K_2Cr_2O_7$; c = SO_3/H_2SO_4; d = KOH; e = $(CH_3)_2SO_4$.

method III. This route is shorter, gives **1** equally well, and has the advantage of avoiding formation of dibromide **5**. Dibromide **5** not only is a potent lachrymator but is also fairly unstable toward moisture. Especially on chromatography over silica, **5** has the tendency to convert into cyclic ether **9**, presumably via partial hydrolysis followed



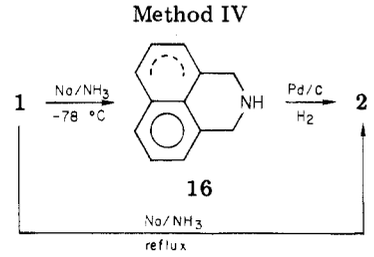
9

by an intramolecular S_N2 reaction. Ether **9** was formed also when $LiAlH_4/AlCl_3$ was used for the reduction of **3** to diol **4**. Method II, adapted from Tochilkin's procedure,[8b] was used when Pd/C catalyzed debenzylation had to be avoided. This was the case when the aromatic skeleton was substituted with halogen, which is also lost under catalytic hydrogenation conditions. Aminolysis of dibromide **5** was performed with liquid ammonia in a pressure bottle at room temperature. Insoluble quaternary salt **7**[8b] was always found as a side product in large quantities.

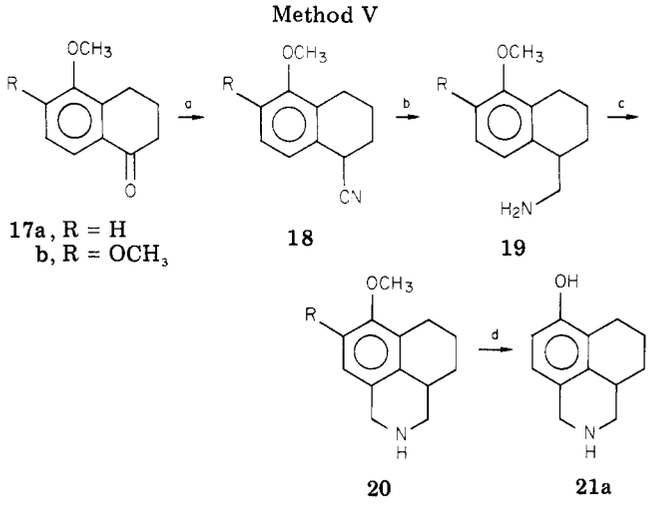
The naphthalic anhydride derivatives necessary for the synthesis of **27**, **32**, **33** and **36** were prepared from bromoacenaphthene[11] and naphthalic anhydride,[11-13] respectively (Scheme II).

Synthesis of 2. The most efficient way to synthesize **2** was through reduction of one of the aromatic nuclei of **1** by a Birch procedure (Scheme III). Sodium in refluxing ammonia transformed **1** efficiently into **2** without formation of side products. The same reaction at lower temperature (−78 °C) gave partially reduced **16**, which could be reduced further to **2** by Pd/C catalyzed hydrogenation.

Scheme III

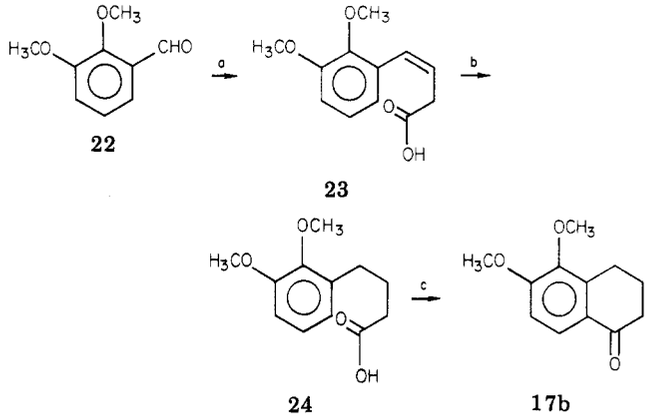


Scheme IV[a]



[a] a = TosMIC = tosylmethylisocyanide; b = $LiAlH_4/AlCl_3$; c = CH_2O/H^+; d = CH_3SO_3H/methionine.

Scheme V[a]



[a] a = $Ph_3P^+CH_2CH_2COOHBr^-$/NaH/Me_2SO/THF; b = Pd/C, H_2; c = PCl_5-$SnCl_4$.

A completely different route was used for some substituted derivatives of **2** (Scheme IV). The key step of this method, which starts with commercially available or easy to prepare tetralones (**17**), is the cyclization with formaldehyde. This reaction is based on the Pictet–Spengler synthesis of isoquinolines. A prerequisite for a successful application of this reaction is the presence of an electron-donating group (e.g., methoxy) on the para position with respect to the site of attack.

The phenol **21a** was prepared from **20a** by cleaving the methyl group with methanesulfonic acid in the presence of methionine.[14] The synthesis of tetralone **17b** is depicted in Scheme V.

(11) J. Cason, A. Weiss, and S. A. Monti, *J. Org. Chem.*, **33**, 3404 (1968).
(12) F. Anselm and F. Zuckmayer, *Ber. Dtsch. Chem. Ges.*, **32**, 3283 (1899).
(13) K. Dziewonski and T. Stolyhwo, *Ber. Dtsch. Chem. Ges.*, **57**, 1540 (1924).
(14) N. Fujui and H. Irie, *J. Chem. Soc., Perkin Trans. 1*, 2288 (1977).

Table I

coupling agents	no.
H_2NCN	25-29
$BrCN/HONH_2$	30-37
$BrCN/N_2H_4$	38, 39
$BrCN/H_2NN(CH_3)_2$	40
$BrCN/N_2H_4/CH_3COCH_3$	41
$H_3CSC(NH_2)=NR$	45-56
$NaN(CN)_2$	57

Coupling Reactions. Benz[*de*]isoquinolines **1** and **2**, as well as their substituted analogues, are useful synthons for the synthesis of a variety of compounds that can be obtained by substitution at the benz[*de*]isoquinoline nitrogen atom with various reagents, such as cyanogen bromide, cyanamide and *S*-methylisothiourea and its congeners. The reaction products formed may be used for further transformations. The coupling agents used and the products formed are denoted in Table I. Most of the benz[*de*]isoquinolines synthesized were crystallized as salts. Table II summarizes the chemical, physical, and pharmacological data of the compounds which were synthesized by one of the methods mentioned above.

Blood Platelet Aggregation Inhibition. Drug effects on blood platelet functions are usually tested in in vitro tests, such as the ADP-, thrombin- and collagen-induced aggregation of blood platelets and the collagen-induced release of serotonin. However, discrepancies are reported between the in vivo and in vitro effectiveness of drugs.[15,16] Technical procedures, such as sampling and centrifugation of the blood, addition of anticoagulants, removal of other blood cells, or loss of circulating effects, interfere with drug effects in blood platelet function tests in vitro.

More reliable results are obtained by using in vivo tests, which are especially of importance when predictions have to be made about the drug's effectiveness in man. A simple and suitable in vivo test may be based on the induction and the monitoring of blood platelet aggregation by intravascular administration of one of the usual aggregation inducers. It is well known that injection of collagen into the blood circulation of healthy experimental animals will lead to a mimicked thrombotic event.[17,18] This effect is primarily due to the lodging of formed aggregates in the capillaries of the lung. This aggregation can be recorded by direct counting of the blood platelets in anticoagulated, peripheral blood. Blood platelet aggregation thus induced was determined in male Wistar rats after ip or po administration of placebo or of drug in a dose of 0.2 (mmol/kg)/day, during 5 days. The right common carotid artery was cannulated with a siliconized cannula, and the collagen suspension was infused via this cannula. Sixty and ninety seconds after the start of the infusion of the collagen, blood samples were collected. All animals were subjected to this procedure in a randomized order. The number of blood platelets was determined in all samples using a Coulter counter. Most compounds showed the greatest activity 60 s after the collagen infusion, except **34** which was significantly active only after 90 s. Statistical evaluation of the results was performed using the analysis of variance. In order to meet the requirements for this analysis, the responses (amounts of blood platelets as percentage of the preinfusion level) were replaced by their logarithms. The final results were expressed as the percentage of change compared with the control. Statistical evaluation was done by a Student *t* test. The experimental results of benz[*de*]isoquinoline derivatives **25–57** are collected in Table II.

Discussion

All the orally active benz[*de*]isoquinolines possess a guanidine or a hydroxyguanidine moiety. Substituents at the guanidine, other than hydroxy, always lead to loss of oral activity and mostly to loss of ip activity. Whether one or two rings (see compounds **1** and **2**) are aromatic seems to be of minor importance. Although the "aromatic" **26** is orally active in contrast with the "saturated" **25**, this trend in general cannot be confirmed (cf. **30** vs. **31**). Substituents at the aromatic ring also do not have a beneficial effect on the oral activity. In most cases, loss of activity is observed (cf. **27** and **28** vs. **26**; **34** and **36** vs. **30** and **31**), or equally active compounds are obtained (**29** vs. **26**; **35** vs. **31**). It may be that the electronic effects of the substituents have an influence on the oral activity, as the unfavorable substituents CH_3 and OCH_3 display an opposite value (σ_{para} = −0.17 and −0.27, respectively)[19] with the more favorable chlorine (σ_{para} = 0.23).[19] However, for definite conclusions in this respect, more substituents are necessary.

On the other hand, it may be of significance that all orally active compounds display a solubility in water of between 2.5 and 12 mg/mL (see Table II). It is likely that resorption plays a role, because the ip activity is found in the whole range of solubility. For instance, the closely related **25** and **26** are both active after ip administration but only the slightly soluble **26** (10 mg/mL) maintains its activity after oral administration, whereas the soluble **25** (60 mg/mL) is devoid of activity after oral administration. Obviously membrane passages, transport, and resorption are limiting factors for blood platelet function modulation in vivo. Intrinsically active compounds, i.e., **25**, **28**, **32**, **33**, **38**, **39**, and **42**, which evidently fulfill the structural requirements for activity, do not reach the blood platelets or do not interact with mechanisms which modulate blood platelet activity, when administered orally. Other factors, e.g., electronic effects, may contribute also to the activity, but the importance of those is unclear.

Experimental Section

The structures of all compounds synthesized were confirmed by IR and NMR spectroscopy. Satisfactory equivalent weights were obtained (at the Analytical Department, Organon, Oss; Head, Drs. L. A. van Dijck) for all end products. Elemental analyses were performed by Dr. W. McMeekin, Analytical Department, Organon, Newhouse, Scotland. We acknowledge the technical assistance of S. F. van Aelst, R. van den Bosch, J. Egberts, A. J. M. de Jong, T. Roeters, M. Herberts, A. J. M. van de Heuvel, and R. Klein (Chemistry Department) and T. G. van Dinther and J. L. J. Remmers (Pharmacology Department).

Synthesis of 2,3-Dihydro-1*H*-benz[*de*]isoquinoline Hydrochloride (1). Method I. Naphthalic anhydride **3** was reduced to diol **4** by $LiAlH_4$ according to the method of Höft et al.,[20] after which **4** was brominated by PBr_3 using the method of Carpino[7] and coupled with benzylamine to **6** according to Ried and Grabosch.[21] Compound **6** (8.93 g, 30.6 mmol) was dissolved in 96% ethanol (700 mL), 10% Pd/C (3.0 g) was added, and the mixture was reduced by hydrogen in a Parr apparatus at a pressure of 275 kPa for 3 h. After filtration of the Pd/C and evaporation of the

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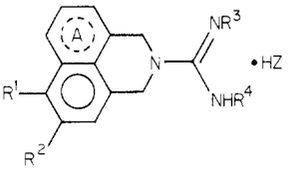
(21) W. Ried and J. Grabosch, *Chem. Ber.*, **91**, 2485 (1958).

Table II



no.	A[a]	R^1	R^2	R^3 [b]	R^4	HZ	mp, °C	anal.	method[c]	sol[d]	% increase[e] ip	% increase[e] po
25	0	H	H	H	H	HCl	>280	C, H, N	III/IV	60	25*	6
26	1	H	H	H	H	HCl	>280	C, H, N, O	III	10	38*	28*
27	0	CH_3	H	H	H	HCl	>280	C, H, N	III/IV	16	tox[f]	16
28	0	OCH_3	H	H	H	HCl	260 dec	C, H, N, O	V	17	44*	−7
29	1	Cl	H	H	H	HCl	>280	C, H, N	II	2.5	tox	22[g]*
30	0	H	H	OH	H	HCl	212	C, H, N, O	III/IV	12	42*	23*
31	1	H	H	OH	H	HCl	>250	C, H, N, O	III	4	36*	23*
32	0	CH_3	H	OH	H	HCl	212	C, H, N, O	III/IV	18	45*	ND[h]
33	1	CH_3	H	OH	H	HCl	233	C, H, N, O	III	5	16*	14
34	0	OCH_3	H	OH	H	HCl	203	C, H, N, O	V	5	70*	8[i]*
35	1	Cl	H	OH	H	HCl	243	H, N, O; C[j]	II	3	44*	18*
36	1	H	OCH_3	OH	H	HCl	206	C, H, N, O	III	18	ND	−5
37	0	OCH_3	OCH_3	OH	H	HCl	200	C, H, N, O	V	>50	30*	ND
38	0	H	H	H	NH_2	HCl	>250 dec	C, H, N	III/IV	60	34*	4
39	1	H	H	H	NH_2	HCl	>250 dec	C, H, N	III	10	28*	6
40	1	H	H	H	$N(CH_3)_2$	HCl	148	C, H, N	III	25	ND	−2
41	0	H	H	H	$N{=}C(CH_3)_2$	HCl	208 dec	C, H, N	III/IV	100	tox	0
42	0	H	H	H	CH_3	fum[k]	239 dec	C, H, N	III/IV	<3	30*	12
43	0	H	H	CH_3	CH_3	fum	189	C, H, N	III/IV	20	2	ND
44	1	H	H	CH_3	CH_3	fum	167	H, N; C[l]	III	25	1	ND
45	0	H	H	C_6H_5	H	fum	228	H, N; C[m]	III/IV	<3	−11	ND
46	0	H	H	C_6H_4-*p*-Cl	H	fum	205	H, N; C[n]	III/IV	<4	ND	7
47	0	H	H	C_6H_4-*p*-OCH_3	H	fum	211	H, N; C[o]	III/IV	<3	tox	7
48	1	H	H	C_6H_4-*p*-OCH_3	H	fum	215	C, H, N, O	III	<5	−2	ND
49	0	H	H	C_6H_4-*p*-NO_2	H	fum	230	C, H, N, O	III/IV	<5	tox	−7
50	0	H	H	C_6H_4-*p*-NH_2	H	fum	246	C, H, N, O	III/IV	<5	tox	8
51	1	H	H	C_6H_4-*p*-NH_2	H	2HCl	256	C, H, N, O[p]	III	60	ND	8
52	0	H	H	C_6H_4-*p*-$N(CH_3)_2$	H	HCl	251	H, N; C[q]	III/IV	4	ND	4
53	0	H	H	C_6H_4-*p*-COOH	H	HBr	>270	H, N; C[r]	III/IV	<3	ND	2
54	0	H	H	C_6H_4-*p*-$CONH_2$	H	HCl	>280	C, H, N	III/IV	<3	ND	7
55	0	H	H	C_6H_4-*p*-SO_2NH_2	H	*s*	211	C, H, N[t]	III/IV	<3	ND	3
56	1	H	H	$COCH_3$	H	HCl	241	C, H, N[u]	III	35	17*	ND
57	0	H	H	CN	H	*s*	181	C, H, N	III/IV	<3	1	ND

[a] Saturated = 0; aromatic = 1. [b] R^3 and R^4 are interchangeable because of tautomerism. [c] Method of synthesis; see text. [d] Solubility in water, in mg/mL, at room temperature. [e] Increase of circulating blood platelets relative to placebo, 60 s after collagen administration unless stated otherwise. [f] Not determined because of toxicity. [g] Three days of ip, followed by 2 days of po administration. [h] Not determined. [i] Only active 90 s after collagen administration. [j] C: calcd, 52.36; found, 53.34. [k] Fumaric acid. [l] C: calcd, 64.21; found, 63.61. [m] C: calcd, 67.79; found, 67.03. [n] C: calcd, 62.51; found, 61.79. [o] C: calcd, 65.89; found, 65.22. [p] Contains 0.45 mol of H_2O. [q] C: calcd, 68.00; found, 67.41. [r] C: calcd, 57.70; found, 56.94. [s] Free base. [t] Contains 0.5 mol of CH_3OH. [u] Contains 0.1 mol of CH_3OH; * = statistically significant ($p < 0.05$).

solvent, 6.31 g (30.6 mmol, 100% yield) of **1** was obtained as a white solid.

Method II. In a typical example, 5.9 g (16.9 mmol) of 1,8-bis(bromomethyl)-4-chloronaphthalene was dissolved in approximately 20 mL of liquid ammonia in a pressure bottle, provided with a magnetic stirring bar. The mixture was stirred overnight at ambient temperature. The ammonia was allowed to evaporate. The residual solid material was taken up in a mixture of ether and 4 N NaOH solution. The insoluble material (quaternary salt **7**) was filtered off, and the aqueous layer was extracted with ether (2 × 100 mL) and dichloromethane (2 × 100 mL). The collected organic layers were dried over Na_2SO_4 and evaporated to dryness, and the oily residue was dissolved in HCl-saturated methanol. After evaporation of the solvent, 2.28 g (9.5 mmol, 56% yield) of crude solid 6-chloro-2,3-dihydro-1*H*-benz[*de*]isoquinoline hydrochloride was obtained. This material was used without further purification.

Method III. To 50 g (254 mmol) of naphthalic anhydride in a round-bottomed flask, with stirrer and dropping funnel, was added 303 mL (2.77 mol) of benzylamine in 25 min. After the addition was completed, the bath temperature was raised to 160 °C and the mixture was stirred for 1 h. The mixture was cooled to 100 °C and poured out into 2.5 L of water under ice cooling. The precipitate was filtered off and washed with water until neutral. The solid was dissolved in dichloromethane, the aqueous layer was separated, and the organic layer was dried over Na_2SO_4 and evaporated to dryness, after which 72 g (251 mmol, 98.5% yield) of **8** was obtained. Compound **8** (34.5 g, 120 mmol) was added portionwise under an atmosphere of nitrogen in 30 min to a suspension of $LiAlH_4$ (13.43 g, 354 mmol) in a mixture of dry toluene (280 mL) and dry ether (560 mL). The mixture was mechanically stirred during 22 h at 50 °C. Under ice cooling, 39 mL of water and 13 mL of a 15% NaOH solution were added. The mixture was stirred for another 2 h, after which the solid material was filtered off. The filtrate was acidified by HCl in methanol, the solvents were evaporated, and the crude reaction product was recrystallized from ethanol: 15.9 g (53.7 mmol, 44.8% yield) of **6** was obtained, which was debenzylated to **1** as described in method I.

Synthesis of 2,3,3a,4,5,6-Hexahydro-1*H*-benz[*de*]isoquinoline Hydrochloride (2). Method IV. Birch reduction of **1**, followed by Pd/C hydrogenation, afforded **2** according to Hückel and Jennewein.[22] The same reaction at refluxing ammonia temperature instead of at −78 °C afforded **2** directly, without the need of subsequent Pd/C hydrogenation.

(22) W. Hückel and C.-M. Jennewein, *Chem. Ber.*, 442 (1963).

Method V. Synthesis of 21a. 5-Methoxytetralone (**17a**; 17.5 g, 0.1 mol) was dissolved in 1.8 L of dry 1,2-dimethoxyethane (DME). Under nitrogen at 0 °C, a solution of 112 g (1 mol) of potassium *tert*-butoxide in 850 mL of dry *tert*-butyl alcohol was added in 30 min. The solution was stirred for another 1.5 h without external cooling. Tosylmethyl isocyanide (TosMIC;[23] 39.0 g, 0.2 mol) in 500 mL of dry DME was added in 4 h. The mixture was stirred overnight, poured out into 4.5 L of brine, and extracted with 3 × 1.5 L of toluene. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was chromatographed on silica with toluene, yielding 13.8 g (73.8 mmol, 74% yield) of **18a**.

Amine **19a** was prepared as follows. A solution of $AlCl_3$ (10.9 g, 82 mmol) in 150 mL of dry ether was added in 10 min to a suspension of 3.12 g (82 mmol) of $LiAlH_4$ in 150 mL of dry ether. Compound **18a** (13.8 g, 73.8 mmol) in dry ether (250 mL) was added in 1 h to the suspension. The mixture was stirred for 2 h at 20 °C. Under ice cooling, 60 mL of water was added and the suspension was stirred for another hour. The precipitate was filtered off and washed with ether. The solid material was taken up in 250 mL of 2 N NaOH solution and 600 mL of ether and stirred for 30 min. The ether was separated from the aqueous layer, the aqueous layer was washed with ether, and the combined ether layers were washed with brine, dried over Na_2SO_4, and evaporated to dryness. Amine **19a** was obtained in a yield of 94% (13.25 g, 69.4 mmol).

Formaldehyde (18.5 mL, 37% aqueous solution) was added in 15 min under stirring to a solution of 14.9 g (78 mmol) of **19a** in 185 mL of methanol. The solution was stirred for 30 min at 50 °C, after which 90 mL of concentrated hydrochloric acid was added in 15 min. The mixture was stirred for another 30 min at 50 °C and poured out into 700 mL of water and 320 mL of 4 N NaOH solution. The product was extracted with 3 × 250 mL of dichloromethane, the extracts were washed with 3 × 300 mL of brine, and the organic layer was acidified with HCl-saturated methanol. The solution was evaporated to dryness and dried by azeotropic distillation of toluene. The crude product was recrystallized from a methanol–ether mixture: yield of **20a** was 77.5% (14.6 g, 60,5 mmol). The phenol **21a** was obtained in 90% yield from **20a** according to the method of Fujui and Irie.[14]

Synthesis of 5,6-Dimethoxy-1-tetralone (17b). A solution of 42.33 g (255 mmol) of 2,3-dimethoxybenzaldehyde (**22**) and 156 g (375 mmol) of (2-carboxyethyl)triphenylphosphonium bromide in 270 mL of dry THF and 270 mL of dry Me_2SO was added under stirring to 26.8 g (655 mmol) of a NaH dispersion (~60%) under a nitrogen atmosphere at a temperature of between −5 and 5 °C. The addition was completed in 2 h, and the mixture was stirred for an additional 5 h at 5 °C and overnight at ambient temperature. The mixture was cooled to 5 °C, and 1750 mL of water was added. The crystals formed were filtered off, and the pH of the filtrate, which has to be ≥8, was checked. If necessary, the pH was adjusted to a correct value by addition of a 4 N NaOH solution. The aqueous solution was washed with ether, after which the pH was brought to 2 by a 4 N HCl solution. The acidic aqueous solution was extracted with ether, which was dried over Na_2SO_4 and evaporated to dryness. A crude product **23**, which contained small amounts of triphenylphosphine oxide, was obtained (60 g). This crude material was dissolved in 200 mL of acetic acid, and 10 g of 5% Pd/C was added. Hydrogenation of this mixture was performed in a Parr apparatus. After separation of the catalyst and evaporation of the solvent, 57.6 g of a slowly crystallizing oil was obtained. This product was cyclized with PCl_5 and $SnCl_4$ according to the method of Oka and Motohashi.[24] After purification on silica gel with an hexane–acetone mixture (9:1, v/v), 36.85 g of **17b** (70% yield based on **22**) was obtained.

Synthesis of naphthalic anhydrides **12** and **15** was performed according to standard procedures (see text). Coupling reactions of the benz[*de*]isoquinoline synthons with cyanamid, cyanogen bromide, and *S*-methylisothiourea were performed with a small excess of coupling reagents in an appropriate solvent. As a typical example, 1 equiv of the free base of **1** or **2** and 1.1 equiv of cyanamid were refluxed in toluene during 3 h. The mixture was evaporated to dryness, dissolved in HCl-saturated methanol, evaporated to dryness again, and recrystallized from ethanol–ether.

Collagen Induced Blood Platelet Aggregation Test. Twenty-four Male Cpb:WU rats (Spf-bred by CPB-TNO, Zeist, The Netherlands), body weight ~200 g, were randomized into two groups. One group was treated with the drug during 5 days in a daily dose of 0.2 mmol/kg ip or po. The other group was treated during that period with placebo. On the 5th day, the animals were anesthetized in a randomized order with sodium pentobarbitone (Nembutal, Abbott, Evry sur Avre, France, 40–50 mg/kg of body weight ip). The right common carotid artery was cannulated with a siliconized cannula (PT 47 or PT 48, Portland Plastics Ltd., Hythe, U.K.). Two subsequent blood samples, each of 0.4 mL of free flowing blood, were collected in plastic tubes containing 20 μL of a 0.25 M EDTA solution. The acidic collagen (0.2 mg of collagen/mL, Horm Chemie, Munich, GFR) was infused during 30 s via the same cannula using a perfusion pump (Braun, Melsungen, GFR, infusion rate 0.5 mL/min). Sixty and ninety seconds after the start of the infusion of the collagen, 0.4-mL blood samples were collected in 20 μL of a 0.25 M EDTA solution as before. Of all blood samples, the number of blood platelets was determined as follows. Anticoagulated blood samples of 10 μL were mixed with 5 μL of Thrombo-oil (Hoek-Loos, Amsterdam, The Netherlands, specific gravity 1.044) in K_2EDTA-coated micropipets and centrifuged for 10 s at 20000 *g* in a microhematocrite centrifuge (Hereaus Christ GmbH, Osterode, GFR). The platelets, in the front layer of thrombo-oil–plasma, were collected by breaking the micropipet and added to 30 mL of Isoton (Coulter Electronics Ltd., Harpenden, U.K.). After careful mixing, the platelets were counted in a Coulter Thrombocounter C (Coulter Electronics Ltd., Harpenden, U.K.).

Solubility. Solubilities were determined in water at pH 5–7 at room temperature.

(23) O. H. Oldenziel, D. van Leusen, and A. M. van Leusen, *J. Org. Chem.* **42**, 3114 (1977).

(24) Y. Oka and M. Motohashi, *Chem. Pharm. Bull.*, **25**, 632 (1977).