

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 13-135212- -5	FECHA: 2014-05-26 17:08:27
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 9
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
JUAN PABLO CADENA SARMIENTO

Asunto: Radicación: 13-135212- -5
 Trámite: 11
 Evento: 378
 Actuación: 519
 Oficio: 6297
 Folios: 9

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2011/070620				
Fecha de Presentación Internacional	22/11/2011				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Rad.13-135212-00000-0000	04/junio/2013
Reivindicaciones:	Rad.13-135212-00000-0000	04/junio/2013
	Rad.13-135212-00001-0000	28/junio/2013
Prioridad: 10382314.2	Rad.13-135212-00000-0000	23/Noviembre/2010

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el presente caso se estudiará la totalidad del capítulo reivindicatorio (reivindicaciones 1- 10).

Título de la solicitud: “DERIVADOS DE FENILAMINA: USOS, PROCEDIMIENTOS DE SINTESIS Y COMPOSICIONES FARMACÉUTICAS”.

El problema planteado en esta solicitud consiste en la necesidad de diseñar compuestos con actividad para la terapia inmunomoduladora.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de fórmula (I) o una sal, profármaco o solvato del mismo.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 31/137, A61K 31/341, A61K 31/137, C07C 211/27, C07D 473/16.

4. De la solicitud de patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

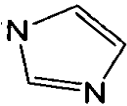
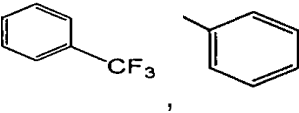
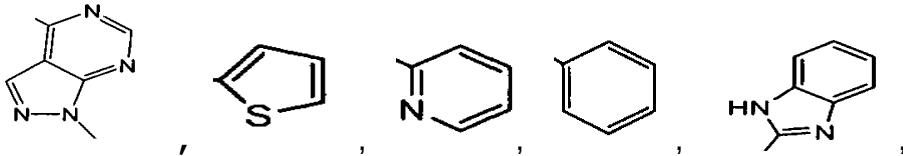
Las reivindicaciones 1 y sus dependientes hacen referencia a un compuesto de fórmula general (I) o una sal, profármaco o solvato del mismo, sin embargo, no se encuentran soportados los métodos, solventes, etc., que permiten llegar a la formación de un solvato o de un profármaco, teniendo en cuenta que el término profármaco comprende muchas estructuras químicas que no están soportadas en la descripción. También mencionan que los sustituyentes del radical R4 pueden ser un heteroarilo sustituido o un arilo sustituido, dichos términos no son concisos porque no se sabe el número de carbonos de los anillos ni cuales y cuantos son los hetroátomos en el caso de los heteroarilos.

La reivindicación 2, no especifica claramente los sustituyentes y su significado.

Las reivindicaciones 3-4, no son claras en su dependencia.

La reivindicación 5 no es clara porque no depende de la reivindicación 4 que menciona algunos grupos heteroarilos sustituidos o no.

Ejemplos de los compuestos soportados con actividades como inhibidores de TNF α , IL4 y 6 α comprobadas

Sustituciones	Soportede los ejemplos presentados
Ph	fenilo
n	2, 3 o 4
m	1
R1	H, CH3
R2	-CH2-
R1 y R2 juntos forman un grupo heteroarilo sustituido o no sustituido	
R3	
R4	  Sustituido con fenilo, metilo, etilo, F
Ra,Rb,Rc,Rd,Re	H, alquilo C1-6, fenilo y trifluorometilo

El solicitante debe definir específicamente la materia y el alcance de la invención a través de las características técnicas esenciales que se encuentren enteramente soportadas en la descripción, por ejemplo con base a los compuestos que presentan la actividad atribuida como los siguientes: 3, 6,8,11,13.

Se requiere al solicitante hacer las aclaraciones necesarias.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 23 de noviembre de 2010, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	articulo	New prnylamine-analogues: investigations of their influence on calciumdependent biological systems	Enero de 1993

D2	US6087346	Sigma receptor ligands and the use thereof	Junio 11 de 2000
D3	articulo	The Reactions Of The Disodium Adduct Of Benzophenone Añil	Mayo 11 de 1966
D4	US007320993	Aryl substituted pyridylalkane, alkene, and alkane carboxamides useful as cytostatic and immunosuppressive agents	Enero 22 de 2008

D1¹ Compuestos derivados difenil alquilamina con actividad como antagonistas de calcio (pages 555-558).

D2² Compuestos fenilalquilamina con alta afinidad por receptores sigma (Cl. 33).

D3³ Revela el compuesto de fórmula (XV, pág.2248).

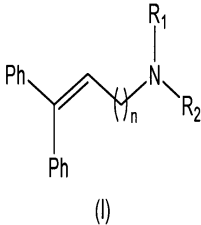
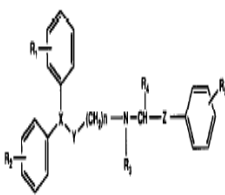
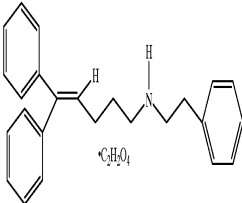
D4⁴ divulga compuestos de fórmula (I) con actividad en diversos tipos de cáncer (indicaciones, cl. 129, ejemplos 114 y 117).

6. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en un compuesto de fórmula (I) según radicado N° Rad.13-135212-00001-0000.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

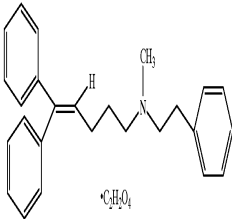
Características esenciales	D1	D2	D3
Compuesto de fórmula (I)	Compuesto de fórmula (I)	Compuestos:	
 O una sal, profármaco o solvato, donde Ph es fenilo; n es 2, 3 ó 4; R1	 Compuesto 50 donde los sustituyentes significan: R1 y R2: H;	 Ph₂C=CH—(CH₂)₃-NH-Ph N,1,1-triphenyl-5-aminopentene-1 (pág. 2248)	

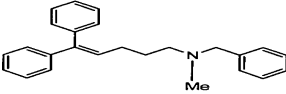
1 Adjunto a concepto

2http://worldwide.espacenet.com/searchResults?compact=false&PN=US6087346&ST=advanced&locale=en_EP&DB=EPODOC

3 Adjunto a concepto

4http://worldwide.espacenet.com/searchResults?compact=false&PN=US7320993&ST=advanced&locale=en_EP&DB=EPODOC

se selecciona del grupo que consiste en hidrógeno y alquilo C1-C6; R2 es un radical de fórmula $[[CH(R3)]_m-R4]$, en la que m es 1; R3, cuando sea apropiado, se selecciona del grupo que consiste en hidrógeno, fenilo y alquilo C1.C6; R4 se selecciona del grupo que consiste en un radical heteroarilo no sustituido, un radical heteroarilo sustituido y un radical arilo sustituido, seleccionándose dichos sustituyentes del grupo que consiste en alquilo C1-C6, arilalquilo C7-C11, fenilo, heteroarilo de 5 o 6 miembros, F, Cl, Br, I, trifluorometilo, ciano, -N(Ra)(Rb), -ORc, -SRd o -C(O)Re; en los que Ra, Rb Re, Rd y Re se seleccionan independientemente de hidrógeno, alquilo C1-C6, fenilo y trifluorometilo; o si R1 y/o R3 son distintos de hidrógeno, entonces R4 también puede ser fenilo no sustituido; o R1 y R2, junto con el átomo de nitrógeno al que están unidos, forman un grupo heteroarilo sustituido o no sustituido, en el que dichos sustituyentes son tal como se definieron anteriormente con la condición de que: 2-[(4,4-difenil-but-3-enilamino)-metil]-fenol, 3-[(4,4-difenil-but-3-enilamino)-metil]-fenol,	X-Y: C=CH; n:2; R3:H; R4:CH3; Z:CH2; R5:H Compuesto 51 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:2; R3:H; R4:CH3; Z:CH2; R5:m-CF3 Compuesto 52 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:2; R3:H; R4:H; Z:CH2; R5:H Compuesto 53 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:2; R3:H; R4:CH3; Z:CH2-CH2; R5:H Compuesto 54 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n: 2; R3: H; R4: H; Z:CH2; R5:/ Compuesto 55 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:3; R3:H; R4:CH3; Z:CH2; R5:H Compuesto 56 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:3; R3:H; R4:H; Z:CH2; R5:H Compuesto 57 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:2; R3:H; R4:H; Z: CH2-CH2; R5:H Compuesto 58 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:2; R3:CH3; R4:H; Z:CH2-CH2; R5:H		
---	--	--	--

5-[(4,4-difenil-but-3-enilamino)-metil]-2-metoxifenol,; 4-[(4,4-difenil-but-3-enilamino)-metil]-2,6-difluoro-feriol, bencil-(5,5-difenil-pent-4-enil)-etil-amina, 6-cloro-9-(4,4-difenil-but-3-enil)-9H-purina, 9-(4,4-difenil-but-3-enil)-9H-purin-6-ilamina, y 5-(4,4-difenil-but-3-enil)-4, 5,6,7-tetrahidro-isoxazolo[4,5-c]piridin-3-ol no estén incluidos en la fórmula (I).  Compuesto 16 (sal de clorhidrato)	Compuesto 60 donde los sustituyentes significan: R1 y R2: H; X-Y: C=CH; n:3; R3:H; R4:H; Z:CH2-CH2; R5:H Tabla I, pág.557		
---	---	--	--

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en los documentos D1, D2 y D3.

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1, D2 y D3.

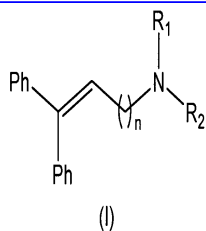
Las reivindicaciones dependientes 2- 10 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

Nivel inventivo (Art18 D486)

La reivindicación 1 consiste en un compuesto de fórmula (I) según radicado N° Rad.13-135212-00001-0000. Modalidades que puedan ser nuevas.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D4
Compuesto de fórmula (I)	Compuesto de fórmula (I)

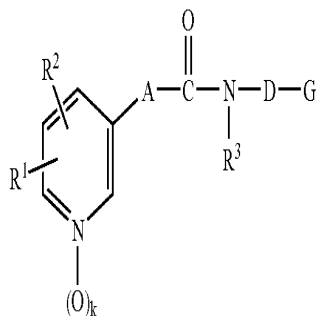


O una sal, profármaco o solvato, donde Ph es fenilo; n es 2, 3 o 4; R1 se selecciona del grupo que consiste en hidrógeno y alquilo C1-C6; R2 es un radical de fórmula $[[CH(R3)]_m-R4]$, en la que m es 1; R3, cuando sea apropiado, se selecciona del grupo que consiste en hidrógeno, fenilo y alquilo C1-C6; R4 se selecciona del grupo que consiste en un radical heteroarilo no sustituido, un radical heteroarilo sustituido y un radical arilo sustituido, seleccionándose dichos sustituyentes del grupo que consiste en alquilo C1-C6, arilalquilo C7-C11, fenilo, heteroarilo de 5 o 6 miembros, F, Cl, Br, I, trifluorometilo, ciano, -N(Ra)(Rb), -ORc, -SRd o -C(O)Re; en los que Ra, Rb, Re, Rd y Re se seleccionan independientemente de hidrógeno, alquilo C1-C6, fenilo y trifluorometilo;

o
si R1 y/o R3 son distintos de hidrógeno, entonces R4 también puede ser fenilo no sustituido;

o
R1 y R2, junto con el átomo de nitrógeno al que están unidos, forman un grupo heteroarilo sustituido o no sustituido, en el que dichos sustituyentes son tal como se definieron anteriormente con la condición de que:

2-[(4,4-difenil-but-3-enilamino)-metil]-fenol,
3-[(4,4-difenil-but-3-enilamino)-metil]-fenol,
5-[(4,4-difenil-but-3-enilamino)-metil]-2-metoxifenol;
4-[(4,4-difenil-but-3-enilamino)-metil]-2,6-difluorofenol,
bencil-(5,5-difenil-pent-4-enil)-etil-amina,
6-cloro-9-(4,4-difenil-but-3-enil)-9H-purina,
9-(4,4-difenil-but-3-enil)-9H-purin-6-ilamina, y
5-(4,4-difenil-but-3-enil)-4, 5, 6,7-tetrahidroisoxazolo [4,5-c]piridin-3-ol no estén incluidos en la fórmula (I).



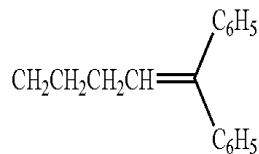
R1 y R2:CH3

K: 0

A: -CH2-CH2-

R3:H

-D-G:



El documento D4 se considera el estado de la técnica cercano a la invención

definida en la reivindicación 1 porque divulga el compuesto de fórmula (I) (cl. 73 y 74) que tiene actividad como antitumoral para diversos tipos de cancer (indicaciones cl.129).

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D4 consiste en que los compuestos de la solicitud son aminas con un grupo **-NH-(CH₂)₃i4-CH=C(Ph)₂** mientras que la anterioridad se refiere a amidas **-C(O)-NH-(CH₂)₃i4-CH=C(Ph)₂**.

No existe evidencia de que al excluir el grupo **-C(O)-** para formar una amina se obtenga un efecto sorprendente.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar el compuesto conocido en D4 para obtener otros compuestos alternativos con actividad como antitumorales”.

Cabe mencionar que en la descripción no existe algún tipo de estudio comparativo mediante el cual se evidencie que los compuestos de la invención presenten un efecto sorprendente frente a los más cercanos de D4 como los son los compuestos 114 y 117 que presentan la misma actividad como antitumorales para diversos tipos de cáncer (indicaciones cl.129).

En consecuencia, la persona del oficio normalmente versada en la materia, podría hacer esta modificación de amidas a amina conocida comúnmente por la persona medianamente versada en la materia⁵ para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Las reivindicaciones dependientes 2-10 no mencionan alguna característica que haga inventiva a la composición de la reivindicación 1, por lo cual se considera que tampoco son inventivas.

7. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	articulo	1-10	Novedad
D2	US6087346	1-10	Novedad
D3	articulo	1-10	Novedad
D4	US007320993	1-10	Nivel Inventivo

⁵ Adjunto al concepto. Química Orgánica Morrison y Boyd, quinta edición 1998 (reacción de Hofmann, pág. 1083-1088).

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-06-03

Elaboró: Lyna Del Carmen Mordecay Dunoyer
Revisó: Gloria Jacqueline Alfonso Rozo

New prenylamine-analogues: investigations of their influence on calcium-dependent biological systems

P Caldirola¹, P Zandberg², R Mannhold³, H Timmerman^{1*}

¹Department of Pharmacochimistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam;

²Organon International BV, Department of General Pharmacology, Oss, The Netherlands;

³Institut für Lasermedizin, Heinrich-Heine-Universität, Düsseldorf, Germany

(Received 23 November 1992; accepted 21 January 1993)

Summary — Chemically, prenylamine belongs to the diphenylalkylamine class. Compounds of this class are calcium antagonists with a broad spectrum of activities due to their influence on both extracellular and intracellular sites. In the present study the calcium antagonistic profile of a recently developed new series of prenylamine analogues has been investigated using different *in vitro* systems. The inhibiting concentrations for the most active compound are $\approx 1.5 \mu\text{M}$; several derivatives are inactive up to a concentration of $10 \mu\text{M}$. Structural modifications towards an increase of lipophilicity make these molecules interact (inhibition) with the intracellular calcium-binding protein calmodulin; for the series no correlation between calcium-blocking and calmodulin antagonistic effects has been found.

prenylamine derivatives / diphenylalkylamines / calcium antagonists / calmodulin antagonists / qualitative structure–activity relationship

Introduction

The plasmalemma is an important factor for the maintenance of cellular functions. The integrity of the plasmalemma is required in order to maintain the ionic gradient between extracellular compartments. The importance of ionic permeation through the cell membrane in response to extracellular stimulation is well confirmed and the role of ions as transducers of an extracellular signal into the cell has been studied extensively [1]. Na^+ , K^+ and Ca^{2+} are examples of ions directly involved in several biological processes [2]. Sodium and potassium play a role in the variation of the membrane potential; calcium is involved in cellular reactions directly or by interacting with factors possessing a key role in many cellular processes. Calcium ions therefore have important functions in stimulation–secretion coupling, excitation–contraction coupling in smooth and skeletal

muscle, cell proliferation [3–5] and platelet aggregation [6]. Because of the broad spectrum of calcium activity, much attention is given to the possibilities of interfering with calcium homeostasis in order to control pathological situations due to abnormal calcium handling.

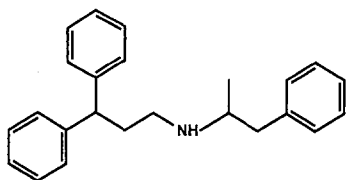
Transmembrane-inward calcium movements occur through distinct classes of calcium channels, classified as voltage-operated (VOC) and receptor-operated (ROC) channels [7]. Changes in membrane potential by electrical stimulation or through agonist–receptor interaction may lead to the activation of the VOC or the ROC respectively. Calcium can also be mobilized from intracellular reservoirs such as the endoplasmic reticulum; in addition, the mitochondria play a role in preventing the so-called calcium overload [8].

Thus calcium ions originating from either extracellular or intracellular sources increase the free cytosolic calcium concentration, thereby activating the distinct calcium-dependent pathways represented in scheme 1.

Cytosolic calcium might directly lead to cellular response; but effects may also result from calcium interactions with certain calcium-binding factors such as calmodulin and troponin-C. Calmodulin [9] and troponin-C [10, 11] are present in smooth muscle and skeletal muscle respectively; both these proteins have a high affinity for calcium.

*Correspondence and reprints

Abbreviations: R: receptor; ROC: receptor-operated-calcium channel; VOC: voltage-operated calcium channel; PIP_2 : phosphatidyl-inositol-bis-phosphate; DG: diacylglycerol; PKC: protein kinase-C; IP_3 : inositol-trisphosphate; ENPR: endoplasmic reticulum; MLCK: myosin-light-chain kinase; PDE: phosphodiesterase.



Scheme 1. The structure of prenylamine.

A Ca_i^{2+} -protein complex is considered as the active species of these factors. Troponin-C interacts with troponin-I, liberating actin from the troponin-I-actin complex (skeletal muscle contraction), while calmodulin mediates the phosphorylation of *eg* myosin light chain kinase (MLCK), which is a necessary step for smooth muscle contraction. Different enzymes such as phosphodiesterase (PDE), glycogen synthetase, $\text{Ca}^{2+}\text{Mg}^{2+}$ -ATPase and adenylate cyclase are also activated upon interaction with the Ca_i^{2+} -calmodulin complex [12–14].

Several pathological disorders such as angina, heart arrhythmias, myocardial infarction and vasospasm are at least in part attributed to an excessive intracellular calcium concentration [2]. Interference with systems by which the intracellular calcium concentration is increased as well as interference with modulating factors by which the action of calcium is mediated might re-establish normal conditions.

Blockade of calcium channels in smooth muscle has been well investigated. Calcium channels are complex structures constituted of membrane proteins of which the 165 kDa polypeptide is considered as the regulatory component of the channel [15]. Several so-called calcium-entry blockers such as verapamil, diltiazem and nifedipine are in clinical use [16]. These compounds represent the 3 main classes of calcium-entry blockers; they block the slow inward calcium current through the VOCs by interacting with specific binding sites at different subunits of the calcium channel [17].

Another group of compounds which modulate Ca-mediated activity is represented by prenylamine (fig 1), fendiline, cinnarizine and pimozone. The compounds can be classified as diphenylalkylamines; their interaction sites are less well-defined than those of the classical calcium-entry blockers [18].

Compounds such as prenylamine interfere not only with the extracellular binding site, but also with the intracellular Ca_i^{2+} -CaM complex [19]. The interaction with the calmodulin complex causes a blockade of calmodulin activity. Pharmacologically the action of this class of compounds is strongest on smooth muscle [20].

Using prenylamine as the lead structure, we have recently developed a new series of prenylamine

analogues with a relatively high capacity to inhibit calmodulin-mediated reactions [21]; synthetic routes for several of the compounds have been previously described [22]. We have now completed this series, which is presented in table I.

We have applied changes at X (where X is S; O; $\text{CH}=\text{CH}_2$), chain extension $(\text{CH}_2)_n$, substitution of the amphetamine moiety by other groups such as phenylethylamine, phenylpropylamine, the cinnamyl group introduction of substituents as F, Cl, CF_3 , CH_3 in the aromatic rings (R_1 , R_2 and R_5). Some compounds were synthesized in which one of the phenyl of the benzhydryl group was omitted or replaced by an alkyl chain (R'_2) (table III).

In the present study we describe the synthesis of several new compounds as well as the *in vitro* pharmacological profile (Ca^{2+} antagonism) of the complete series. The structure-activity relationships are discussed from a qualitative point of view.

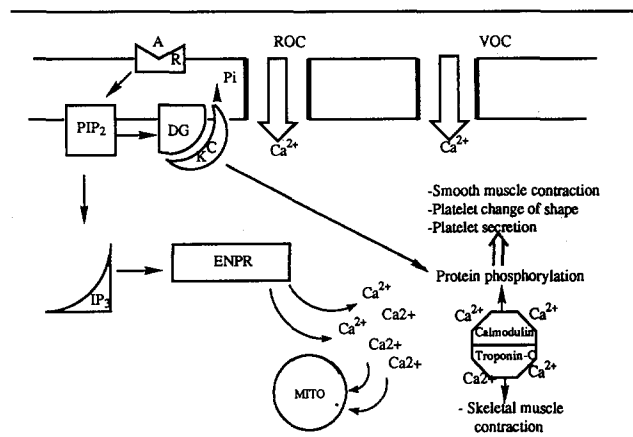
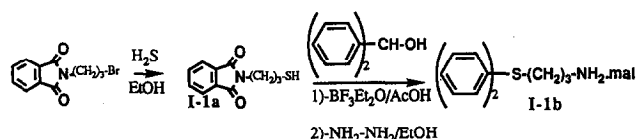


Fig 1. Calcium liberated upon agonists (A)-receptor (R) interaction or electrical/potassium stimulation reaches the cytosol through the receptor-operated (ROC) and/or voltage-operated (VOC) calcium channels. The agonist-receptor interaction leads to the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) with the formation of 1,2-diacylglycerol (DG) and inositol-1,3,5-trisphosphate (IP_3). Kinase-C (KC) activated by DG contributes to the activation of ROC and phosphorylates other proteins. IP_3 mediates intracellular calcium liberation from the endoplasmic reticulum (ENPR). Calcium interacts with troponin-C, promoting the skeletal muscle contraction. The interaction of calcium with calmodulin induces *eg* smooth-muscle contraction and platelet shape change. The platelet reactions result from the synergism between calmodulin-dependent protein kinase and kinase-C activation. Mitochondria (MITO) are present to prevent calcium overload.



Scheme 4. Synthesis of the intermediate **I-1b**.

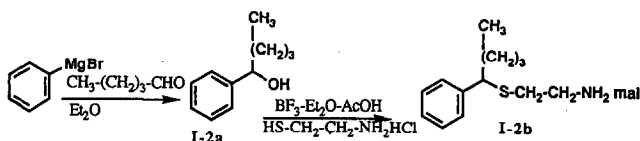
the benzhydrol with **II-c** under basic conditions using sodium amide.

In schemes 4 and 5 the syntheses of benzhydrylthio-analogues and non-benzhydryl-derivatives are shown. The preparation of the benzhydryl-thiopropyl intermediate **I-1b** was started by treating γ -bromophthalimide with hydrogen-sulphide under basic conditions [24] to give the mercaptane **I-1a**. This mercaptane was condensed with benzhydrol and subsequently hydrolysed under basic conditions to give the primary amine **I-1b**, which was isolated as its maleate.

The intermediate compound in which one phenyl of the benzhydryl moiety has been replaced by an alkyl-chain was obtained as shown in scheme 5. 1-Phenylpentanol **I-2a**, prepared by a Grignard reaction between phenylmagnesium bromide and valeraldehyde, was alkylated with cysteamine to give the intermediate compound **I-2b**.

Pharmacology

The interference of this class of compounds with VOCs was evaluated from dose-response curves obtained by inhibition of K^+ -induced contractions of rabbit aortic strips and by inhibition of [^3H]-nitrendipine binding to a cerebral cortex protein preparation. The influence on intracellular calcium-mediated pathways was established by determining the concentration of the compounds necessary to cause 50% noradrenaline-induced (NA, 10^{-6} M) contractions of rabbit aortic strips and the 50% inhibition of collagen and thrombin-induced platelet aggregation. In order to obtain a better insight into the sites of action, different platelet models such as platelet-rich plasma (PRP,



Scheme 5. Synthesis of the intermediate **I-2b**.

rabbit), washed platelet (WSP, rabbit) and human skinned platelet have been used.

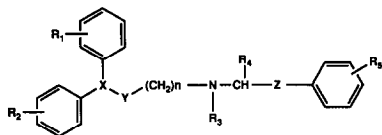
The interference with calmodulin as a potential intracellular site of action was studied directly by measuring inhibition of PDE activation (see *Experimental protocols*).

Results

Previously the affinity of a number of compounds belonging to this new series of prenylamine-analogues for the voltage operated calcium-channels was established by determining their K_d s in displacing [^3H]-nitrendipine from a cerebral cortex membrane preparation from rat or guinea pig. In this system the K_d s have been found to be in the μM range [22]. In the present paper the functional activity of the compounds has been evaluated by establishing their potencies to inhibit the contractions of isolated aortic strip preparations induced by either 40 mM K^+ or 1 μM NA. In this preparation, NA raises the cytosolic calcium concentration by stimulating the liberation of calcium from the endoplasmic reticulum. Additionally, NA increases the calcium influx through ROCs. On the other hand, potassium activates the calcium-inward current through VOCs. The results presented in table II show that both potassium- and NA-induced contractions are completely inhibited at different concentrations by several of our compounds. The most potent compounds act at a concentration $\approx 1 \mu M$. However, some of them are inactive at a concentration up to 10 μM .

The property of the compounds to block platelet aggregation has been studied in several models using different inducers. Rabbit platelet-rich plasma (PRP), gel-filtrated platelets (GFP) and washed platelet model (WSP) were aggregated with collagen and thrombin. When thrombin was used as the aggregation inducer, the GFP model was used only in order to avoid clot formation as a result of THR-mediated polymerization of the fibrinogen to fibrin [25] which is present in the PRP system. Albumin is present in both the PRP- and GFP-systems, whereas in the washed platelet model (WSP) it is absent. The activity of the tested compounds in WSP was considerably higher than in normal platelets. All of the tested compounds have calmodulin-blocking properties as they inhibit the calmodulin-mediated activation of phosphodiesterase (PDE) at concentrations which are in the μM range. Some of them are as potent as most of the active calmodulin antagonists described in the literature such as phenothiazines and naphthalenesulphonamides and calmidazolium [26].

Inositoltrisphosphate (IP_3) was used as an intracellular inducer of aggregation in skinned human platelets. Due to the limited supply of human platelets we could not test all compounds in this model.

Table II. Pharmacological effects of a series of prenylamine analogues (6-65).

N°	(platelet aggregation tests)			(spasmolytic activities)				Σf	
	PRP Coll	GSP IP ₃ THR Coll	WSP	K _d Ca ²⁺ NA	K ⁺	PDE			
Prenyl	65	119	-	0.115	23	9	14	6.64	
6	37	17	11	8	4.0	10	2.9	4.2	6.71
7	-	>33	7	>12.5	1.1	>10	>10	2.3	7.85
8	>100	40	-	8	0.3	>10	>10	1.43	8.27
9	57	>50	7	-	1.24	3.7	2.0	3.0	6.19
10	31	18	16	6	1.01	10	2.4	4.60	7.23
11	>50	>46	-	4	0.3	10	3.6	3.0	7.43
12	57	66	-	5	0.5	>10	4.0	2.25	7.74
13	>100	>20	-	+12.5	0.74	>10	4.2	1.45	7.64
14	>100	>30	-	+12.5	1.5	>10	>10	1.85	8.71
15	>70	>50	-	5	1.0	4.6	1.6	6.3	8.23
16	20	28	-	10	3.00	>10	>10	2.80	7.16
17	-	45	-	8	0.42	>10	2.2	2.35	6.63
18	>100	49	-	4	0.4	>10	5.9	2.30	7.05
19	84	45	-	6	0.114	>10	3.8	2.25	8.12
20	>50	>50	-	+12.5	3.75	>10	>10	3.83	7.78
21	>50	>50	-	9	0.12	>10	>10	1.15	8.2
22	47	14	20	-	1.0	-	-	7.90	7.23
23	>50	42	7	-	0.309	>10	4.7	2.60	7.12
24	10	-	-	5.0	1.06	5.6	1.9	6.2	5.67
25	>50	-	-	3.4	0.34	-	-	0.70	7.75
26	-	-	-	-	0.21	-	-	1.0	-
27	>50	-	-	3.0	0.5	>10	>10	1.43	7.33
28	-	-	-	-	0.08	-	-	0.75	7.75
29	12.5	-	-	9.0	0.51	3.8	1.4	6.10	6.13
30	10	-	-	9.0	0.54	>10	2.8	3.0	6.65
31	>50	>50	-	-	0.307	-	-	4.50	7.14
32	>50	50	-	-	0.125	>10	>10	>50	8.70
33	>50	>50	-	-	0.135	>10	>10	>50	8.07
34	34	24	19	5	3.0	4.1	1.5	16.90	5.62
35	29	17	9	10	1.44	4.9	1.3	17.00	6.04
36	21	15	10	8	2.43	2.6	2.1	4.70	6.14
37	>100	>50	7	5	0.11	10	3.0	3.0	6.77
38	>50	41	-	4	0.216	2.8	1.6	8.7	5.62
39	86	>50	4	4.0	1.04	1.3	0.5	4.20	5.52
40	>100	>30	-	5	1.02	5.7	1.7	3.90	6.14
41	63	40	7	-	0.944	2.6	0.7	1.85	6.56
42	>50	-	-	>50	0.82	3.4	1.1	9.50	5.62
43	>50	>50	-	-	0.3	6.8	2.0	13.00	5.62
44	>50	>33	-	-	0.423	4.8	4.4	2.90	6.66
45	>50	/	-	0.407	0.407	>8	1.6	0.75	7.19
46	75	50	3	-	3.2	3.0	1.1	2.45	5.96
47	-	-	-	1.5	1.5	2.4	0.33	10	6.05
48	40	-	-	10	0.502	>10	>10	2.80	7.43
49	25	-	2.0	0.8	-	>10	>10	8.7	5.56
50	57	62	4	7.0	3.0	2.8	2.4	2.40	7.08
51	>100	>50	10	+12.5	2.32	>10	>10	0.95	7.85
52	53	72	3	-	2.3	2.4	2.1	3.20	6.56
53	79	76	2	7.0	3.0	4.8	2.8	1.35	7.60
54	10	42	-	3.0	0.5	7.4	3.0	4.15	6.04
55	>50	>50	-	-	0.718	10	2.49	1.55	7.6
56	>50	>50	-	-	1.02	>10	2.6	2.55	7.08
57	>50	>50	-	-	1.2	38	4.1	1.95	7.08
58	-	-	-	-	1.5	1.1	1.5	2.30	7.51
59	>50	>50	-	-	1.0	6.9	6.3	1.10	7.01
60	>50	45	-	-	1.02	-	-	1.25	7.6
61	31	68	-	4	1.3	1.9	1.4	6.60	7.16
62	35	54	8	4	0.370	10	5.4	1.18	8.30
63	>42	45	-	-	0.5	2.9	1.9	5.50	6.64
64	46	>33	-	4	0.470	2.4	1.4	3.50	7.68
65	>50	42	/	-	0.445	3.6	1.5	3.40	6.79

The values represent the 50% inhibition of platelet aggregation and of noradrenalin (NA)- and potassium (K⁺)-induced smooth muscle contractions. Inhibition of calmodulin-mediated activation of phosphodiesterase (PDE) and displacement of [³H]-nitrendipine (K_d) are included. The IC₅₀- and the K_d-values are expressed in μM. The measure of lipophilicity is given by Σ_f.

In table II, it can be seen that several but not all the compounds show a moderate effect against thrombin and collagen-induced aggregation; some of them display a rather high activity against the IP₃-induced effect.

Qualitative structure-activity relationships

The mechanism of action of calcium antagonists of the diphenylalkylamine type has so far not been clearly established. The pharmacological profile is determined by both the calcium entry blocking activity and the influence on cytosolic calcium-mediated reactions. The series of prenylamine analogues presented in this paper was therefore prepared in order to obtain insight into the structural features required for the different actions.

The effect of the structural modifications was assessed by evaluating the affinity of these compounds for the calcium channel in the displacement of [³H]-nitrendipine, by PDE interference with calmodulin-mediated activation, by the inhibitory effects on vasoconstriction in functional studies (K⁺- and NA-induced contractions) of aortic rings in comparison with the inhibition of collagen- or thrombin-induced platelet aggregation.

First we examined the effect of the changes in the chains flanking the nitrogen atom; the general formula has been presented in table I.

Chain related to -X-Y-(CH₂)_n-

The extension of the chain between the benzhydryl moiety and the nitrogen by insertion of sulphur, oxygen or carbon atoms leads to compounds with increased inhibitory activity on NA- and K⁺-induced contraction, as well as an increased capacity for inhibiting PDE activation.

Some compounds are also more active against collagen- and thrombin-induced platelet aggregation while their potency in [³H]-nitrendipine displacement does not differ from that of prenylamine.

The compounds may be divided into subclasses: sulphur (6-33); oxygen (39-49); unsaturated (50-60) and saturated (61-65). A selectivity towards voltage-operated calcium channels was observed in compounds belonging to the sulphur class which showed a higher inhibitory capacity on K⁺-induced contractions. Most of the oxygen- and the carbon-containing compounds interact with both VOCs and ROCs, as they inhibit K⁺- and NA-induced contractions at the same concentration range. However, some members of the oxygen and the carbon sets possess some selectivity for ROCs over VOCs.

A few examples with longer 5-member chains are given: 29, 30, 49, 55, 56 and 60. These compounds show a higher activity against collagen-induced platelet aggregation and [³H]-nitrendipine displacement (29, 30, 49), while such a lengthening is

deleterious for the inhibition of smooth-muscle contractions induced by both NA and K⁺ as well as for the inhibition of calmodulin-mediated PDE activation. The lengthening of the chain mainly increases the activity against collagen-induced platelet aggregation, as shown in comparison by the following pairs: **29/9**; **30/15** and **49/42**.

Changes related to Z

Extension of the chain in this part of the molecule by adding an additional methylene group and also the introduction of unsaturation brought about by the allyl-group increases the potency in displacing [³H]-nitrendipine 3- and 2-fold seen when compounds **6**, **10**, **15**, **17** of the sulphur-, **34**, **40**, **42** of the oxygen- and **50**, **53**, **57**, **59** of the unsaturation sets respectively are compared, while no influence in the saturated subclass was observed.

Changes in the amphetamine moiety

Replacement of the amphetamine moiety, which is present in the lead structure, by a phenylethylamine moiety hardly affects the activity with regard to the inhibition of induced vasoconstriction and to the affinity for the calcium-channel (K_d). However, a slight reduction in the activity against collagen- and thrombin-induced platelet aggregation was observed (**6/9**, **13/16**, **45/49**, **50/52**, **53/57**).

Because no significant differences in inhibition of induced vasoconstriction and in inhibition of platelet aggregation were seen by comparing compounds either containing or lacking the methyl in the α -position to the nitrogen atom, we may conclude that the methyl group of the amphetamine moiety is not essential for the activities. The phenylethyl group seems to be a good alternative for the amphetamine substituent.

Changes in the aromatic groups

Substitution in both the benzhydryl and phenyl moieties may significantly influence the profile of these compounds. The influence of substitution in the benzhydryl moiety was studied in the sulphur and oxygen subclasses. In the sulphur set, going from H to F to Cl, a decrease in activity and selectivity for ROCs compared to VOCs as well as a decrease in the capacity for displacing [³H]-nitrendipine was found (**10**, **13**, **14**). The introduction of the fluorine-atom does not influence these parameters for the oxygen derivatives. In both the oxygen and sulphur classes, the methyl substitution neither affects the inhibition of platelet aggregation nor the inhibition of smooth muscle contraction in comparison to that of the unsubstituted compounds **34**, **36**, **44**. However, a 13- and 2-fold increase in activity was observed in the capacity to inhibit PDE activation and to displace [³H]-nitrendipine when **34** and **44** are compared.

Comparable activity patterns exist between the methyl-substituted compound **36** and the non-substituted amphetamine homologue **47**. The lengthening of the Z-chain in **47** seems to compensate for the absence of a substituent in the benzhydryl moiety.

The electron-withdrawing CF₃-group in the phenyl ring (amphetamine moiety) plays a more evident influence on the pharmacological profile of these compounds than the substitution in the benzhydryl moiety. Substitution by CF₃ is deleterious both in inhibition of platelet aggregation and smooth muscle contractions (**6/7**, **35/45**, **50/51**, **61/62**, **20/17**, **48/41**).

The introduction of CF₃ in the amphetamine aromatic group increases the capacity to displace [³H]-nitrendipine and to interact with calmodulin. In the *p-p'*-bis-(fluorophenyl)thio-benzhydryl derivative (**9/28**) the change of the position of CF₃ in amphetamine from *meta* to *ortho* results in a 10-fold increase of the affinity for the calcium-channel.

Methylation of the nitrogen atom

The introduction of the methyl substituent on the nitrogen atom changes neither the calcium-entry blocking activity nor the capacity to inhibit platelet aggregation (by comparison: **26/25**, **31/10**; **47/42**, **48/45**, **32/8**, **33/13**, **57/58**). This conversion of secondary to tertiary amine by methylation has a strong influence on the inhibition of PDE as can be seen from the drop in activity of **32** and **33** when compared to the secondary amines **8** and **13**.

Chirality

All the chiral compounds were synthesized in racemic form. The *d*-isomer **43** of the racemic analogue **34** does not show any difference in vasorelaxant activity; however, this isomer has a 10- and 4-fold higher capacity to displace [³H]-nitrendipine and inhibit calmodulin respectively, while the racemic mixture is slightly more active on platelet aggregation.

General

This general qualitative structure-activity analysis led us to the hypothesis that molecular lipophilicity (Σ_f) [27] may play an important role in the mechanism of action of these compounds. The pharmacological data of the 4 sets of compounds were analysed in relation to lipophilicity. Linear regression analysis of the oxygen sets reveals a significant correlation coefficient ($r = 0.8$) for lipophilicity related to inhibition of vasoconstriction (K⁺- and NA-induced contractions). For the negative slope of the curve-fitting, quantitative analysis showed that the vasorelaxant activity decreased with lipophilicity. The sulphur- and the unsaturated groups included the most lipophilic compounds. The good correlation coefficient ($r = 0.9$) obtained by correlating calmodulin-inhibiting potency with lipophilicity for the unsaturated derivatives

confirmed that lipophilicity plays an important role in the interaction of these compounds with calmodulin. No correlation was obtained when lipophilicity and inhibition of smooth muscle contractions of both sulphur and the unsaturated groups were compared.

The narrow IC_{50} range found for the sulphur group in all the activities did not permit an accurate correlation analysis to be made.

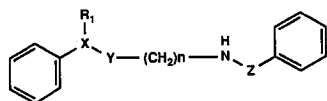
The increase in lipophilicity by aromatic substitution together with the lengthening of the n and z chains decreases the potency and selectivity for the calcium-entry blocking action. A proper substitution pattern which gives an optimal lipophilicity ranging between Σ_f values of 5 to 6 seems to be required in order to obtain higher potency in inhibiting smooth muscle contraction. A few molecules in our oxygen class such as **34**, **35**, **39**, **45**; one example in the sulphur (**9**) and in the saturated (**52**) class possess such a characteristic. Moreover, lipophilic compounds in the sulphur and in the saturated class, represented by **25** and **45**, are the most potent calmodulin inhibitors.

The influence on smooth-muscle contractions and on platelet aggregation is more dependent on variations in the amphetamine moiety; however, because the potencies in the several tests can be modulated by a proper change in the whole molecule we conclude that this whole molecule is the pharmacophore. Moreover, the presence of 2 bulky extremities as anchor-sites is required for calmodulin antagonistic activity. This hypothesis is confirmed by the absence of significant pharmacological effects in compounds lacking the benzhydryl moiety (table III).

Discussion

Calcium involved in smooth muscle contractions originates from both intra- and/or extracellular sources. Compounds which are calcium antagonists and/or calmodulin blockers may obtain their inhibitory effects by interfering with both systems.

Table III. Pharmacological effects of a series of prenylamine analogues (**6–65**).



N°	R ₁	X-Y	n	Z	PRP Coll	WSP Coll	KdCa ²⁺ PDE
66	CH ₃ (CH ₂) ₂	CH-S	2	CH ₂ -CH ₂	>50	50	3.7
67	H	CH-CH ₂	1	CH ₂ -CH ₂	>50	38	5.7
68	H	CH-CH ₂	2	CH ₂ -CH=CH	>50	13	/

Our present series of diphenylalkylamines of the prenylamine type are moderately active as calcium antagonists and are potent calmodulin inhibitors.

From previous studies, it appeared that in our series there was no correlation between the 2 types of activities. We were therefore interested in studying the pharmacological profile of our enlarged series of compounds in several functional tests in an attempt to differentiate between calcium-blocking and calmodulin-antagonizing properties. Smooth-muscle preparation and platelets were selected for this purpose, as it is known that calcium and calmodulin play a very important role in contractile responses in both systems [28].

As shown in table II, most of our compounds inhibit the K⁺-induced slow phasic contraction which is due to an increase in the calcium-inward current [29, 30], in the μ M concentration. The same range of potency was previously found in the inhibition of [³H]-nitrendipine binding to cerebral cortex [22], which seemed to demonstrate that the calcium channel VOC might be the pharmacologically relevant site of action of these compounds. However, a comparable inhibition of contraction was found when NA was used as the contracting agent. Noradrenaline obtains its effect by increasing the intracellular calcium current through ROCs, but also by liberating calcium from intracellular stores [31].

By comparing the effects of these 2 tests it was found that the NA/K⁺ IC_{50} antagonism ratio approaches unity. An intracellular site of action therefore seems more probable. However, an α -adrenoceptor-mediated effect cannot be excluded.

With the assumption that both intra- and extracellular effects of our compounds might be present, we continued our investigation on platelet aggregation using different models. When platelets are extracellularly stimulated by agents such as THR and collagen, calcium is liberated from the dense tubuli system which leads to the secretion of certain factors and to the changes in the shape of the platelets (and eventually to aggregation).

There are several indications that extracellular calcium does not play a primary role in these reactions, although a calcium fraction bound at the extracellular site of the membrane is needed to extend the already initiated aggregation process [32]. As VOCs are absent in platelets, typical calcium-entry blockers such as DHPs and diltiazem are not anti-aggregating agents. However, compounds like verapamil and bepridil do antagonize aggregation of platelets induced by THR; it has therefore been suggested that their inhibitory activity may stem from their interactions with α_2 -receptors and from anti-serotonergic effects [8].

In the responses occurring in both the muscle and non-muscle systems, calmodulin is involved as an

active Ca_i^{2+} -CaM-complex. Myosin light chain phosphorylation is one of the several processes activated by this complex. The phosphorylated myosin light chain kinase (MLCK) regulates the actin-myosin interaction, which is an essential step for the change of shape of platelets and the subsequent aggregation.

All our compounds are rather weak inhibitors of THR- and collagen-induced platelet aggregation. However, when IP_3 was used as the inducer of the skinned platelet-reaction, the compounds tested in the system showed a much higher potency. IP_3 and diacylglycerol (DG) are important second messengers of the phosphatidyl pathway (scheme 1). DG activates a protein kinase C which phosphorylates a 40 000-Da protein, while IP_3 is the cytosolic mediator for intracellular calcium mobilization [33] leading to the Ca_i^{2+} -CaM-complex which phosphorylates a 20 000 Da protein myosin light chain. The synergism between intracellular mediators causes the full physiological response which consists of a change in platelet shape and an additional release of platelet constituents such as serotonin and thromboxane A_2 . As our compounds interfere with the IP_3 -induced aggregation, these compounds appear to act intracellularly.

The discrepancy in the activities of the compounds in the applied platelet models might be due to several reasons. There is a major difference between the conditions of the THR/collagen and IP_3 -models: whereas albumin is present in the THR and collagen models, it is absent in the IP_3 model. We considered that the possibility of inactivity in the first 2 models is caused by the binding of our compounds to albumin, thus lowering their free extracellular concentration. Moreover, as diphenylalkylamines are lipophilic in character, they may encounter difficulties in crossing the cell membrane [31]. In order to determine which aspect was involved, we used washed platelets as the fourth model using collagen as the extracellular inducer; in this model no albumin was present. Our compounds were found to be markedly more potent in this system than in platelets in rich plasma. The order of inhibitory potency in IP_3 and WSP was the same as that in smooth muscles and much higher than that in normal platelets. We therefore assume that the activity of our compounds originates from an interaction with an intracellular calcium-mediated pathway and that the inactivity in the PRP might be due to their interaction with the plasma protein.

All members of the present series were tested for calmodulin-blocking activity using PDE as the Ca_i^{2+} -calmodulin activated enzymatic system. The compounds inhibit the phosphorylation of purified PDE [34] with IC_{50} values in the submicromolar range. Their potential capacity of interfering with the Ca_i^{2+} -calmodulin complex may therefore be considered as

part of their anti-aggregatory and inhibitory smooth muscle-contraction properties.

Diphenylalkylamines have a considerable lipophilic character [33]. Lipophilicity is one of the prerequisites for the interaction with calmodulin; in fact, we have found that there is a correlation between calmodulin-blocking activity and lipophilicity [21]. However, lipophilicity might also increase the affinity of these molecules for plasma proteins such as albumin. While the former interaction contributes to their pharmacological profile, the latter phenomenon will reduce their activity. Moreover, because of their lipophilic character, these compounds may accumulate within the membrane phospholipids and indirectly influence other membrane receptor proteins. This influence can be considered as part of their mechanism of action.

The comparison between binding and functional studies would be useful in order to determine structure-activity relationships. No correlation has been found between the activities in the different systems.

The affinities for the calcium channel and for calmodulin are positively influenced by the same structural parameters such as the introduction of the CF_3 and the steric effect as seen with the *d*-isomer of racemate 34; however, the same structural variables have no effect on the inhibition of smooth muscle contractions; and if there is any effect, it is negative.

The first relationship regarding the affinity for calmodulin and for the calcium channel may suggest the existence of certain similarities in the binding sites involved in the interaction of these compounds at both calcium channel and calmodulin, whereas the discrepancy found by analyzing the results obtained in functional studies may be explained by the fact that these lipophilic compounds might disrupt the membrane structure and change the properties of the interaction sites. Therefore difficulties may be expected in detecting the affinity binding sites in functional studies.

The regulatory mechanism controlling the cytoplasmic-calcium concentration is very complex; this observation limits the possibility to clearly define a mechanism of action for our compounds. The testing procedures used during this study suggest both extra- and intracellular sites of action. The lipophilicity directs their action to an intracellular compartment, as interference with calmodulin. The compounds also interfere with VOC-mediated processes such as K^+ -stimulated contractions, at a higher concentration, however, than the DHP; they also inhibit [^3H]-nitrendipine binding, which seems to indicate a lipophilic calmodulin-like calcium-binding protein the presence of which has been suggested as a subunit at the calcium-channel [35]. This possibility is not disproved by the absence of correlation between

calmodulin inhibition and inhibition of smooth-muscle contractions. The absence of correlation may be attributed to the inability of the compounds to pass through the membrane in intact cells.

The present class of diphenylalkylamines is characterized by a broad spectrum of activity in the calcium-mediated pathways. More detailed pharmacological studies are required in order to determine whether the members of this series can be considered as cardiovascular drug candidates.

Experimental protocols

Chemistry

Materials

Reagents, starting materials and solvents were purchased from commercial suppliers. Melting points were obtained on a Mettler FP5 apparatus. ^1H -NMR spectra were recorded on a Bruker WH-90 and a WH-200 and chemical shifts are given in ppm. Mass spectra were obtained with a Finnigan MAT 90 (San Jose, CA, USA).

The synthesis of the prenylamine analogues **6–21**, **34–42**, **50–53** and **61–64** has been previously reported [22]. The synthesis and some chemical properties of the additional new derivatives **22**, **23**; **43–49**, **55–60** and **66–68** new intermediates are presented. The compounds were prepared by reductive amination of the corresponding ketones and aldehydes with the corresponding benzhydrylalkylamines (X-Y: CH-CH₂) and benzhydrylalkylaminoethers (X-Y: CH-S) in methanol or tetrahydrofuran (Method A). The oxygen- (X-Y: CH-O) and unsaturation-containing (X-Y: C=CH) compounds were prepared by alkylation of the different amines with the corresponding benzhydrylalkyl-bromoethers in methyl-isobutylketone (Method B).

All the compounds were isolated by flash column chromatography using a gradient mixture of petroleum/ether (40:60) and ethyl-acetate saturated with ammonia gas as eluent. The secondary amines and the tertiary amine were transformed into their maleic and oxalic salts respectively, which were crystallized from a mixture of ether and methanol (1%).

*1-Methyl-N-{2-[α -(4-methylphenyl)benzylthio]ethyl}-2-phenylethyl-amine maleate **22***

Prepared according to Method A from: *N*-{2-[α -(4-methylphenyl)benzylthio]-ethylamine maleate and phenylacetaldehyde; yield: 75%.

^1H -NMR (CDCl₃) δ : 1.2 (d; 3H J = 6.7, CH₃); 2.3 (s, 3H, *p*-CH₃); 2.7 (dd; 2H J = 13.3, Ph-CH₂); 2.75–3.4 (m; 5H, CH₂-N, CH₂-S, CH-N); 5.3 (s; 1H, CH-S); 6.25 (s; 2H, mal); 7.0–7.35 (m; 14H, arom); 8.75–9.2 (bs; 1.5H, NH); HRMS (C₂₅H₂₉NS); found: 375.2015; calc: 375.2021 (M⁺); mp: 118–120°C.

*1-Methyl-N-{2-[bis(4-fluorophenyl)methylthio]ethyl}-2-phenylethyl-amine maleate **23***

Prepared according to Method A from: *N*-{2-[bis(4-fluorophenyl)methylthio]-ethylamine maleate and phenylacetone; yield: 70%.

^1H -NMR (CDCl₃) δ : 1.2 (d; 3H J = 6.7, CH₃); 2.75 (t; 2H J = 7.3, CH₂-Ph); 2.95–3.5 (m; 5H, CH₂-CH₂-N-CH); 5.15 (s; 1H, CH-S); 6.3 (s; 2H, mal); 7.0 (t; 4H J = 8.0, arom); 7.15–7.4 (m; 9H, arom); 9.0 (bs; 2H, NH); HRMS (C₂₄H₂₅F₂NS); found: 397.1699; calc: 397.16751 (M⁺); mp: 165–167°C.

*N-[(2-Diphenylmethylthio)ethyl]benzylamine maleate **24***

Prepared according to Method A from: *N*-2-(diphenylmethylthio)ethylamine hydrochloride and phenylacetaldehyde; yield: 12%.

^1H -NMR (CDCl₃) δ : 2.65 (t; 2H J = 6.3, CH₂-S); 2.95 (t; 2H J = 6.3, CH₂-N); 4.05 (s; 2H, N-CH₂-Ph); 5.05 (s; 1H, CH-S); 6.2 (s; 2H, mal); 7.0–7.5 (m; 15H, arom); HRMS (C₂₂H₂₃NS); found: 333.153; calc: 333.1551 (M⁺); mp: 147.6–149.3°C.

*N-{2-[Bis(4-fluorophenyl)methylthio]ethyl}-2-[(3-trifluoromethyl)-phenyl]ethylamine maleate **25***

^1H -NMR (CDCl₃) δ : 2.75 (t; 2H J = 7.3, CH₂-Ph); 3.0–3.35 (m; 6H, CH₂-N-CH₂, CH₂-S); 5.2 (s; 1H, CH-S); 6.25 (s; 2H, mal); 6.95 (t; 4H J = 8.0, arom); 7.25–7.55 (m; 8H, arom); HRMS (C₂₄H₂₂F₃NS); found: 451.139; calc: 451.1393 (M⁺); mp: 129–131.1°C.

Compound **25** was prepared by alkylation (Method B; yield: 60%) of 2-[bis(4-fluorophenyl)methylthio]ethylamine with 2-(3-trifluoromethylphenyl)ethylbromide described as below.

*Synthesis of 2-(3-trifluoromethylphenyl)-ethyl bromide **4***

N-2-(3-Trifluoromethylphenyl)-ethanol (5 g, 0.026 mol) was refluxed overnight in 50 ml of a 3:7 mixture of H₂SO₄/HBr 48%.

The reaction mixture was cooled and neutralized with aqueous K₂CO₃ (1 N). The bromide was extracted with ether (3 x 50 ml), dried over Na₂SO₄, filtered and concentrated to yield a brown oil. *In vacuo* distillation (54°C, 0.1 mm Hg) afforded the pure bromide as a colorless oil (85%).

^1H -NMR (CDCl₃) δ : 3.0 (t; 2H J = 7.3, Ph-CH₂); 3.44 (t; 2H J = 7.3, CH₂-Br); 7.20–7.78 (m; 4H, arom); GS/MSD; m/z : 252.90 (M⁺, 0.013%); 172.00 (M⁺-HBr, 100%).

*2-(2-Trifluoromethylphenyl)ethyl bromide **4** R₅: *o*-CF₃*

This was obtained by bromination of the corresponding alcohol 2-[2-(trifluoromethyl)-phenyl]-ethylalcohol, as described above (bp: 80°C *in vacuo* distillation, 0.1 mm Hg).

^1H -NMR (CDCl₃) δ : 3.4 (dt; 4H J = 13.5, CH₂-CH₂-Br); 7.20–7.78 (m; 4H, arom).

*N-Methyl-N-{2-[bis(4-fluorophenyl)methylthio]ethyl}-2-(3-trifluoromethylphenyl)-ethylamine oxalate **26***

^1H -NMR (CDCl₃) δ : 2.25 (s; 3H, CH₃-N); 2.4–2.5 (m; 2H, CH₂-Ph); 2.5–2.6 (m; 4H, CH₂-S; CH₂-N); 5.15 (s; 1H, CH-S); 7.0 (t; 4H J = 10, arom); 7.3–7.5 (m; 8H, arom); HRMS (C₂₅H₂₄F₃NS); found: 465.154; calc: 465.1550.

The tertiary amine **26** was prepared by methylation of **25** according to the method below (scheme 3): secondary amine **25** (6.3 mmol) was added with cooling, to formic acid (15.7 mmol, 90%) followed by the addition of formaldehyde (7.0 mmol, 37% aqueous solution). The mixture was kept at 100°C overnight. HCl (1 N) was added and the aqueous solution was evaporated under reduced pressure. The colourless residue was quenched with water. The reaction mixture was partitioned between aqueous NaOH (0.6 mol/l) and ether. The ether phase was dried over Na₂SO₄ and concentrated. The tertiary amine was isolated by column chromatography using light petroleum 40–60/ethyl acetate (8:2) as eluent (yield: 80%). TLC (SiO₂ PE-EtOAc-NH₃ 80:20-sat), R_f 0.45. The free base was transformed into its oxalate, mp: 163.4–165°C.

*N-[(2-Diphenylmethylthio)-ethyl]-2-(2-trifluoromethylphenyl)-ethylamine maleate **27***

Prepared according to Method B from: *N*-2-(diphenylmethylthio)-ethylamine and 2-(2-trifluoromethylphenyl)ethyl bromide; yield: 15%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.75–3.0 (m; 4H, $\text{CH}_2\text{-Ph}$, $\text{CH}_2\text{-N}$); 3.0–3.25 (m; 4H, $\text{CH}_2\text{-S}$, $\text{CH}_2\text{-N}$); 5.2 (s; 1H, CH-S); 6.3 (s; 2H, mal); 7.1–7.51 (m; 14H, arom); HRMS ($\text{C}_{24}\text{H}_{24}\text{F}_3\text{NS}$); found: 415.158; calc: 415.1581 (M^{+}); mp: 145.1–146.4°C.

N-{2-[Bis(4-fluorophenyl)methylthio]ethyl}-2-(2-trifluoromethylphenyl)-ethylamine maleate **28**

Prepared according to *Method B* from: *N*-2-[bis(4-fluorophenyl)-methylthio]ethylamine and 2-(2-trifluoromethylphenyl)-ethyl bromide; yield: 20%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.8 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 3.15 (t; 2H J = 7.3, $\text{CH}_2\text{-S}$); 3.2 (s; 4H, $\text{CH}_2\text{-N-CH}_2$); 5.2 (s; 1H, CH-S); 6.3 (s; 2H, mal); 7.05 (t; 4H J = 8.0, arom); 7.15–7.5 (m; 12H, arom); HRMS ($\text{C}_{24}\text{H}_{22}\text{F}_5\text{NS}$); found: 451.138; calc: 451.1393 (M^{+}); mp: 149.4–151.3°C.

N-3-[(Diphenylmethylthio)propyl]-2-phenylethylamine maleate **29**

Prepared according to *Method A* from: *N*-3-(diphenylmethylthio)propylamine maleate and phenylacetaldehyde; yield: 30%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.95 (qu; 2H J = 8.0, $-\text{CH}_2-$); 2.45 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 2.9–3.35 (m; 6H, $\text{CH}_2\text{-S}$; $\text{CH}_2\text{-N-CH}_2$); 5.15 (s; 1H, CH-S); 6.3 (s; 2H, mal); 7.17–7.45 (m; 15H, arom); 9.4–9.6 (bs; 1.5H, NH); HRMS ($\text{C}_{24}\text{H}_{27}\text{NS}$); found: 361.183; calc: 361.186 (M^{+}); mp: 123.2–124.8°C.

N-3-[(Diphenylmethylthio)propyl]-3-phenylpropylamine maleate **30**

Yield: 30%; $^1\text{H-NMR}$ (CDCl_3) δ : 2.0 (qu; 4H J = 7.3, $2\times\text{-CH}_2-$); 2.45 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 2.7 (t; 2H J = 7.3, $\text{CH}_2\text{-S}$); 2.9–3.2 (m; 4H, $\text{CH}_2\text{-N-CH}_2$); 5.15 (s; 1H, CH-S); 6.3 (s; 2H, mal); 7.0–7.5 (m; 15H, arom); 9.1–9.6 (bs; 1.5H, NH); HRMS ($\text{C}_{25}\text{H}_{29}\text{NS}$); found: 375.203; calc: 375.2022 (M^{+}); mp: 117.1–118.3°C.

Compound **30** was prepared from *N*-3-(diphenylmethylthio)propylamine and 3-phenylpropionaldehyde according to *Method A*.

Synthesis of phthalimidopropylthiol I-1a

A mixture of potassium hydroxide (1.75 g, 32 mmol) and phthalimidopropylbromide (6.7 g, 25 mmol) in ethanol (75 ml), saturated with H_2S gas (3.4 g, 0.1 mol), was heated for 5 h at 120°C in an autoclave.

The reaction mixture was quenched with water (100 ml). The precipitate consisting of the phthalimidopropylthiol was filtered (mp: 45.3–45.9°C).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.3 (qu; 2H J = 6.7, CH_2), 3.4 (t; 2H J = 6.7, Br- CH_2); 3.9 (t; 2H J = 6.7, Phth- CH_2); 7.65–8.0 (m; 4H, arom).

Phthalimidopropylthiol (4.9 g, 0.022 mol) and benzhydrol (4.05 g, 0.022 mol) were dissolved in acetic acid (20 ml), followed by the addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (3 ml). The reaction mixture was heated at 90°C for 15 min. The acids were evaporated and the residue was taken up with water (50 ml) and the organic material was extracted with CH_2Cl_2 and washed with a Na_2CO_3 solution (0.1 N). The organic phase was separated, dried with Na_2SO_4 and evaporated to dryness. A sample taken for $^1\text{H-NMR}$ gave the following spectrum in CDCl_3 δ : 2.3 (qu; 2H J = 6.3, CH_2), 2.4 (t; 2H J = 6.3, S- CH_2); 3.8 (t; 2H J = 6.3, Phth- CH_2); 5.2 (s; 1H, CH-S); 7.0–7.6 (m; 4H, arom) corresponding to *N*-(3-diphenylmethylthio)-3-phthalyl propyl amide.

Synthesis of 3-(diphenylmethylthio)propylamine maleate I-1b

N-[3-(Diphenylmethylthio)propyl]phthalimide (7 g, 0.018 mol) was dissolved in ethanol (50 ml), followed by an addition of hydrazine (1.73 g, 2.2 ml of 80% water solution, 0.054 mol). The reaction mixture was stirred overnight at room

temperature. The solvent was evaporated. The residue was resuspended in a NaOH (1 N) aqueous solution. The organic material was extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated to an oil. The free base was converted into its maleate salt (yield: 75%); mp: 132.2–134°C.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.85 (qu; 2H J = 6.7, CH_2), 2.4 (t; 2H J = 6.7, S- CH_2); 3.05 (t; 2H J = 6.7, N- CH_2); 5.1 (s; 1H, CH-S); 6.15 (s, 2H, mal); 7.0–7.6 (m; 8H, arom).

1-Methyl-N-[2-(diphenylmethylthio)ethyl]-*N*-methyl-3-(phenylpropyl)-amine oxalate **31**

Prepared by methylation of **10**; yield: 70%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.9 (qu; 2H J = 8.0, $-\text{CH}_2-$); 2.55 (s; 3H, $\text{CH}_3\text{-N}$); 2.6–2.75 (m; 4H, $\text{CH}_2\text{-Ph}$, $\text{CH}_2\text{-S}$); 2.8–3.1 (m; 4H, $\text{CH}_2\text{-N-CH}_2$); 5.15 (s; 1H, CH-S); 7.05–7.45 (m; 15H, arom); HRMS ($\text{C}_{25}\text{H}_{29}\text{NS}$); found: 375.2042; calc: 375.2415 (M^{+}); mp: 164–165°C.

1-Methyl-N-[2-[bis-(4-fluorophenyl)methylthio]ethyl]-*N*-methyl-2-(3-trifluoromethylphenyl)ethylamine oxalate **32**

Prepared by methylation of **8**; yield: 80%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.0 (d; 3H J = 7.3, CH_3-); 2.2 (s; 3H, $\text{CH}_3\text{-N}$); 2.25–3.0 (m; 5H, $\text{CH}_2\text{-CH}_2\text{-N-CH}$); 5.2 (s; 1H, CH-S); 7.05 (t; 4H J = 8.0, arom); 7.35–7.6 (m; 8H, arom); HRMS ($\text{C}_{26}\text{H}_{26}\text{F}_3\text{NS}$); found: 479.1881; calc: 479.1706 (M^{+}); mp: 169.4–170.8°C.

1-Methyl-N-[2-[bis-(4-fluorophenyl)methylthio]ethyl]-*N*-methyl-3-phenylpropylamine oxalate **33**

Prepared by methylation of **13**; yield: 80%. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.05 (d; 3H J = 6.6, CH_3-); 1.5–2.0 (m; 2H, CH_2); 2.4–2.7 (m + s; 3H, CH_3 + 5H, $-\text{CH}_2\text{-Ph}$, $\text{CH}_2\text{-N-CH}$); 3.1 (t; 2H J = 6.6, $\text{CH}_2\text{-S}$); 5.5 (s; 1H, CH-S); 7.0–7.5 (m; 13H, arom). HRMS ($\text{C}_{26}\text{H}_{29}\text{F}_2\text{NS}$); found: 425.1957; calc: 425.1989 (M^{+}); mp: 167.6–169.7°C.

N-[2-(α -*n*-Butylbenzylthio)ethyl]-2-phenylethylamine maleate **66**

$^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (t; 3H J = 7.3, CH_3-); 1.2–1.4 (m; 4H, $2\times\text{CH}_2$); 1.8 (q; 2H J = 7.3, CH_2); 2.65 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 2.6–3.2 (m; 6H, $\text{CH}_2\text{-S}$, $\text{CH}_2\text{-N-CH}_2$); 3.75 (t; 1H J = 7.3, CH-S); 6.3 (s; 2H, mal); 7.1–7.4 (m; 15H, arom); HRMS ($\text{C}_{21}\text{H}_{29}\text{NS}$); found: 327.203; calc: 327.2021; mp: 112.0–115.5°C.

The non-benzhydryl derivative **66** was prepared by the reductive amination (*Method A*; yield: 23%) of phenylacetaldehyde with 2-(*n*-butylbenzylmethylthio)ethylamine maleate.

Synthesis of 1-phenylpentanol I-2a

Bromobenzene (52.3 g, 0.5 mol), dissolved in ether (150 ml), was added to magnesium (11.65 g, 0.5 mol) suspended in anhydrous ether (100 ml). Valeraldehyde (53 ml, 0.5 mol) was slowly added to the Grignard reagent prepared above. After stirring the reaction mixture for 30 min HCl (1 N) was added to destroy the unreacted Grignard reagent. The organic phase was washed with NaOH (0.01 N), separated and dried over Na_2SO_4 and concentrated under reduced pressure (yield: 87%).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.85 (t; 3H J = 7.3, CH_3-); 1.2–1.4 (m; 4H, $2\times\text{CH}_2$); 1.9 (m; 2H, $\text{CH}_2\text{-C-Ph}$); 2.8 (s; 1H, OH); 4.58 (t; 1H J = 7.3, CH-O); 7.1–7.33 (m; 5H, arom).

Synthesis of 2-(n-butylbenzylmethylthio)ethylamine maleate I-2b

1-Phenylpentanol (30.4 g, 0.19 mol) was dissolved in glacial acetic acid (150 ml). 2-Mercaptoethylamine hydrochloride (22.7 g, 0.2 mol) was added, followed by the addition of trifluoroborate etherate (25.8 ml, 0.21 mol). The reaction mixture was heated to 80°C for 30 min. After cooling, water

was added (50 ml), followed by the addition of a potassium-carbonate concentrated solution (pH > 11). The free base was extracted with ether and the organic phase was separated, dried over sodium sulphate and evaporated to dryness. The compound was isolated by column chromatography using petroleum ether/ethylacetate (6:4) saturated with ammonia as a mobile phase (yield: 20%). The free base was converted into maleate (mp: 110.7–112.5°C).

¹H-NMR (CDCl₃) δ: 0.84 (t; 3H *J* = 7.3, CH₃-); 1.15–1.36 (m; 4H, 2 × CH₂); 1.78–1.98 (m; 2H, CH₂-C-Ph); 2.25–2.49 (m; 2H, CH₂); 2.72 (t; 2H *J* = 7.3, CH₂-S); 3.79 (t; 1H *J* = 7.3, CH-S); 6.3 (s; 2H, mal); 7.17–7.38 (m; 5H, arom).

N-{α-[2-(4-Methylphenyl)benzhyloxy]ethyl}-3-phenylpropylamine maleate **42**

Prepared according to *Method B* from: α-[2-(4-methylphenyl)-benzhyloxy]ethyl bromide and 3-phenylpropylamine; yield: 65%.

¹H-NMR (CDCl₃) δ: 2.10 (q; 2H *J* = 7.3, -CH₂-); 2.65 (t; 2H *J* = 7.3, Ph-CH₂); 3.08 (t; 2H *J* = 7.3, CH₂-N); 3.15–3.3 (m; 2H *J* = 7.3, CH₂-N); 3.7 (t; 2H, CH₂-O); 5.5 (s; 1H, CH-O); 6.2 (s; 2H, mal); 7.05–7.4 (m; 15H, arom); 9.3–9.6 (bs; 1H, NH); HRMS (C₂₄H₂₉NO); found: 358.2202; calc: 358.2170 [M⁺⁺+1]; mp: 137–139.1°C.

(*d*)-1-Methyl-*N*-[2-(phenylmethoxy)ethyl]-2-phenylethylamine maleate **43**

Prepared according to *Method B* from: 2-(phenylmethoxy)ethyl bromide and (*d*)-1-methyl-2-phenylethylamine; yield: 80%.

¹H-NMR (CDCl₃) δ: 1.3 (d; 3H *J* = 6.3, CH₃-); 2.8 (dd; 1H *J* = 13.5, Ph-CH); 3.15–3.9 (m; 6H, CH₂-N, CH₂-O, CH-Ph, CH-N); 5.38 (s; 1H, CH-O); 6.2 (s; 2H, mal); 7.05–7.45 (m; 15H, arom); 9.0–9.6 (bs; 1H, NH); HRMS (C₂₄H₂₉NO); found: 346.2125; calc: 346.2162 [M⁺⁺+1]; mp: 163–165°C.

1-Methyl-*N*-[2-[bis(4-methylphenyl)methoxy]ethyl]-2-phenylethylamine maleate **44**

Prepared according to *Method A* from: *N*-2-[bis(4-methylphenyl)-methoxy]ethylamine maleate and phenylacetaldehyde; yield: 75%.

¹H-NMR (CDCl₃) δ: 1.3 (d; 2H *J* = 6.3, CH₃-); 2.25 (s; 6H, 2 × *p*-CH₃); 2.9 (dd; 2H *J* = 9.0, Ph-CH₂); 3.1–3.7 (m; 5H, CH₂-CH₂-N-CH); 3.8 (t; 2H *J* = 4.3, CH₂-O); 5.4 (s; 1H, CH-O); 6.2 (s; 2H, mal); 7.05–7.4 (m; 13H, arom); 8.4–9.0 (bs; 1H, NH); HRMS (C₂₆H₃₁NO); found: 373.2382; calc: 373.2406 [M⁺⁺+1]; mp: 152–154°C.

1-Methyl-*N*-[2-[bis(4-fluorophenyl)methoxy]ethyl]-2-(3-trifluoromethylphenyl)-ethylamine maleate **45**

Prepared according to *Method A* from: 2-[bis(4-fluorophenyl)-methoxy]ethylamine hydrochloride and phenylacetaldehyde; yield: 20%.

¹H-NMR (CDCl₃) δ: 1.3 (d; 3H *J* = 6.7, CH₃-); 2.85 (dd; 1H *J* = 13.3, Ph-CH); 3.2–3.7 (m; 4H, CH-Ph, CH-CH₂-N); 3.8 (t; 2H *J* = 6.0, CH₂-O); 5.35 (s; 1H, CH-O); 6.2 (s; 2H, mal); 6.95 (t; 4H *J* = 8.0, arom); 7.15–7.55 (m; 8H, arom); 9.4–10 (bs; 1H, NH); HRMS (C₂₅H₂₅F₅NO); found: 450.188; calc: 450.1856 [M⁺⁺+1]; mp: 135.7–137.5°C.

N-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-3-phenyl-2-propenylamine maleate **46**

Prepared according to *Method A* from: *N*-2-[bis(4-fluorophenyl)-methoxy]ethylamine hydrochloride and 3-phenyl-2-propenylaldehyde; yield: 50%.

¹H-NMR (CDCl₃) δ: 3.25 (t; 3H *J* = 5.3, CH₂-N); 3.7 (t; 2H *J* = 5.3, O-CH₂); 3.9 (d; 2H *J* = 8.0, =C-CH₂); 5.45 (s; 1H,

CH-O); 6.2 (s; 2H, mal); 6.3 (dt; 1H *J* = 8.0, *J* = 16.7, -CH=C-Ph); 6.65 (d; 1H *J* = 16.7, Ph-CH=); 7.0 (t; 4H *J* = 8.0, arom); 6.15–7.5 (m; 9H, arom); 9.2–9.5 (bs; 1H, NH); HRMS (C₂₄H₂₄F₃NO); found: 380.1796; calc: 380.1780 [M⁺⁺+1]; mp: 147–149°C.

N-[2-(Diphenylmethoxy)-ethyl]-*N*-methyl-3-phenylpropylamine oxalate **47**

Prepared by methylation of **42**; yield: 10%.

¹H-NMR (CDCl₃) δ: 2.05 (qu; 2H *J* = 8.0, CH₂); 2.6 (t; 2H *J* = 8.0, Ph-CH₂); 2.75 (s; 3H, N-CH₃); 3.0–3.2 (m; 2H, CH₂-N); 3.25–3.4 (m; 2H, CH₂-N); 3.7–3.85 (m; 2H, CH₂-O); 5.35 (s; 1H, CH-O); 7.0–7.4 (m; 15H, arom); HRMS (C₂₅H₂₉NO); found: 359.226; calc: 359.2249; mp: 111.2–112°C.

1-Methyl-*N*-[2-[bis(4-fluorophenyl)methoxy]ethyl]-*N*-methyl-2-(3-trifluoromethylphenyl)phenylethylamine oxalate **48**

Yield: 20%. ¹H-NMR (CDCl₃) δ: 1.2 (d; 3H *J* = 7.3, CH₃); 2.6 (t; 1H *J* = 13.3, Ph-CH); 2.9 (s; 3H, N-CH₃); 3.3–3.55 (m; 3H, CH₂-N, CH-Ph); 3.75–4.0 (m; 3H, CH₂-O, CH-N); 5.40 (s; 1H, CH-O); 6.9–7.6 (m; 12H, arom); 9.8–10.7 (bs; 1H, NH); HRMS (C₂₆H₂₆F₅NO); found: 463.193; calc: 463.1935 (M⁺⁺); mp: 126.1–128.5°C.

Compound **48** was prepared from the coupling reaction between 4,4-di-*F*-benzhydrol (2.10 g, 0.15 mol) and 1-methyl-*N*-(2-chloroethyl)-*N*-methyl-2-(3-trifluoromethylphenyl)ethylamine **II-c** (prepared as below) (2.56 g, 9.2 mmol) in toluene (100 ml), in the presence of sodium amide (0.4 g, 10 mmol). The reaction mixture was refluxed for 2 h (scheme 3). The solvent was evaporated, the residue was taken up in dichloromethane (150 ml), washed with water (3 × 50 ml). The organic phase was separated, dried (Na₂SO₄) and concentrated. The compound was purified on silica using ethylacetate/petroleum ether 40–60 (1:9) previously saturated with ammonia as eluent. The free base was transformed into the oxalate. Crystallization from methanol/ether (1:9) afforded to the desired compound with a yield of 14%.

Synthesis of N-[2-[1-methyl-2-(3-trifluoromethylphenyl)]-aminoethanol **II-a**

A solution of 3-(trifluoromethyl)-phenylacetone (5.0 g, 0.024 mol), aminoethanol (1.46 g, 0.024 mol) and NaBH₄CN (1.58 g, 0.025 mol) in tetrahydrofuran (100 ml) was stirred at room temperature for 5 days. The solvent was evaporated, the residue was dissolved in dichloromethane (100 ml) and washed with water (3 × 100 ml). The organic phase was separated, dried over Na₂SO₄, filtered and concentrated. The compound was purified over silica by flash chromatography using methanol/petroleum ether 40–60 (1:9). The desired compound was obtained with a yield of 43%.

¹H-NMR (CDCl₃) δ: 1.08 (d; 2H *J* = 6.3, CH₃); 2.0–2.43 (bs; 1H, OH); 2.58–3.13 (m; 5H, Ph-CH₂, CH-N-CH₂); 3.64 (t; 2H *J* = 5.4, CH₂-O); 7.32–7.76 (m; 4H, arom).

Synthesis of N-methyl-*N*-[1-methyl-2-(3-trifluoromethylphenyl)-ethylaminoethanol **II-b**

N-[2-[1-Methyl-2-(3-trifluoromethyl)phenyl]ethyl]aminoethanol (3.4 g, 0.013 mol) was dissolved in formaldehyde (25 ml, 38% aqueous solution) and formic acid (25 ml, 98%). The reaction mixture was refluxed overnight. The solutions were evaporated and an aqueous solution of NaOH (0.1 N 50 ml) was added. The organic material was extracted with dichloromethane. The organic phase was dried (Na₂SO₄) and concentrated. The residue was purified on a silica column with methanol as eluent to afford 2.6 g (75%) of the pure compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.04 (d; 3H J = 6.3, CH_3); 2.32 (s; 3H, N-CH_3); 2.52–3.07 (m; 6H, $\text{Ph-CH}_2\text{-CH-N-CH}_2$); 5.34 (t; 2H J = 5.4, $\text{CH}_2\text{-O}$); 7.28–7.70 (m; 4H, arom).

Synthesis of 1-methyl-N-(2-chloroethyl)-N-methyl-2-(3-trifluoromethyl)phenylethylamine HCl II-c

N-Methyl-1-methyl-[2-(3-trifluoromethyl)phenyl]aminoethanol (2.4 g, 9.2 mmol), dissolved in toluene (50 ml), was treated with thionyl chloride (9.19 g, 10 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated with the excess of thionyl chloride. The residue containing 2.56 g (88%) of the chloride derivative was used in the successive step without further purification.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (d; 3H J = 6.3, CH_3); 2.91 (s; 3H, N-CH_3); 3.28–3.96 (m; 5H, $\text{Ph-CH}_2\text{-CH-N-CH}_2$); 4.18 (t; 2H J = 6.3, CH_2Cl); 7.45–7.76 (m; 4H, arom).

N-[3-(Diphenylmethoxy)propyl]-3-phenylpropylamine maleate 49
Prepared according to *Method B* from: 3-(diphenylmethoxy)propyl bromide and 3-phenylpropylamine; yield: 10%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.9 (qu; 2H J = 6.0, $-\text{CH}_2-$); 2.05 (qu; 2H, $-\text{CH}_2-$); 2.6 (t; 2H J = 6.7, Ph-CH_2); 2.9–3.1 (m; 2H, N-CH_2); 3.1–3.3 (m; 2H, $\text{CH}_2\text{-N}$); 3.55 (t; 2H J = 6.0, $\text{CH}_2\text{-O}$); 5.35 (s; 1H, CH-O); 6.3 (s; 2H, mal); 7.0–7.4 (m; 15H, arom); 9.1–9.3 (bs; 1H, NH); HRMS ($\text{C}_{25}\text{H}_{29}\text{NO}$); found: 359.226; calc: 359.2249 (M^+); mp: 112.8–114.9°C.

N-(4,4-Diphenyl-3-butenyl)-benzylamine maleate 54

Prepared according to *Method B* from: 4,4-diphenyl-3-butenyl bromide and benzylamine; yield: 21%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.55 (q, 2H J = 8.0; C=CH_2); 2.9–3.1 (m; 2H, N-CH_2); 4.15 (s; 2H, $\text{Ph-CH}_2\text{-N}$); 6.0 (t; 1H J = 8.0, CH=C-Ph_2); 6.15 (s; 2H, mal); 7.0–7.45 (m; 15H, arom); 9.45–9.95 (bs; 1H, NH); HRMS ($\text{C}_{23}\text{H}_{23}\text{N}$); found: 313.183; calc: 313.1830 (M^+); mp: 155.7–157.3°C.

1-Methyl-N-(5,5-diphenyl-4-pentenyl)-2-phenylethylamine maleate 55

Prepared according to *Method B* from 5,5-diphenyl-4-pentenyl bromide and 1-methyl-2-phenylethylamine; yield: 60%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.1 (d, 3H J = 7.2; CH_3); 1.5–2.0 (m; 4H, CH_2 , $\text{CH}_2\text{-Ph}$); 2.2–3.5 (m; 5H, $\text{CH}_2\text{-CH}_2$, N-CH); 5.9 (t; 1H J = 7.2, $\text{Ph}_2\text{-C=CH-}$); 6.25 (s; 2H, mal); 6.9–7.35 (m; 15H, arom); 8.9–9.5 (bs; 1H, NH); HRMS ($\text{C}_{26}\text{H}_{29}\text{N}$); found: 355.2263; calc: 355.23 (M^+); mp: 139–140°C.

N-(5,5-Diphenyl-4-pentenyl)-2-phenylethylamine maleate 56

Prepared according to *Method B* from: 5,5-diphenyl-4-pentenyl bromide and 2-phenylethylamine; yield: 60%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.9 (qu, 2H J = 7.3; $-\text{CH}_2-$); 2.15 (q; 2H J = 7.3, $\text{CH}_2\text{-C=}$); 2.9–3.1 (m; 4H, $\text{CH}_2\text{-N}$, $\text{CH}_2\text{-Ph}$); 3.15–3.3 (m; 2H, $\text{CH}_2\text{-N}$); 5.95 (t; 1H J = 7.3, $\text{Ph}_2\text{-C=CH-}$); 6.35 (s; 2H, mal); 7.0–7.4 (m; 15H, arom); 9.2–9.5 (b; 1H, NH); HRMS ($\text{C}_{25}\text{H}_{27}\text{N}$); found: 341.2163; calc: 341.2161 (M^+); mp: 129–131°C.

N-(4,4-Diphenyl-3-butenyl)-3-phenylpropylamine maleate 57

Prepared according to *Method B* from: 4,4-diphenyl-3-butenyl bromide and 3-phenylpropylamine; yield: 50%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.9–2.2 (m; 2H, CH_2); 2.5–2.8 (m; 4H, CH_2 , $\text{CH}_2\text{-Ph}$); 2.8–3.2 (m; 4H, $\text{CH}_2\text{-N-CH}_2$); 6.0 (t; 1H J = 7.2, $\text{Ph}_2\text{-C=CH-}$); 6.15 (s; 2H, mal); 7.0–7.4 (m; 15H, arom); 9.0–9.6 (b; 1H, NH); HRMS ($\text{C}_{25}\text{H}_{29}\text{N}$); found: 342.2185; calc: 342.2221 (M^++1); mp: 148.4–150°C.

N-(4,4-Diphenyl-3-butenyl)-N-methyl-3-phenylpropylamine maleate 58

Prepared according to methylation of **57**; yield: 30%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.0 (qu; 2H J = 7.3, CH_2); 2.25 (s; 3H, $\text{CH}_3\text{-N}$); 2.4–2.7 (m; 4H, $-\text{CH}_2\text{=C}$, $-\text{CH}_2\text{-Ph}$); 2.8–3.0 (m; 2H, $\text{CH}_2\text{-N}$); 3.0–3.2 (m; 4H, $\text{CH}_2\text{-N}$); 6.0 (t; 1H J = 7.2, $\text{Ph}_2\text{-C=CH-}$); 7.0–7.5 (m; 15H, arom); HRMS (EI) ($\text{C}_{26}\text{H}_{29}\text{N}$); found: 334 [M-H]; HRMS (CI, NH_3); found: 356 (M^++1); 355 is the exact mass.

N-(4,4-Diphenyl-3-butenyl)-3-phenyl-2-propenylamine maleate 59
Prepared according to *Method B* from: 4,4-diphenyl-3-butenyl bromide and 3-phenyl-2-propenylamine; yield: 50%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.55 (q; 2H J = 7.3, CH_2); 3.05 (t; 2H J = 7.3, CH_2); 3.7 (d; 2H J = 7.3, $\text{N-CH}_2\text{-C=}$); 6.0 (t; 1H J = 7.3, $\text{Ph}_2\text{-C=CH-}$); 6.15 (s; 2H, mal); 6.2 (dt; 1H, J = 6.7, CH=C-Ph); 6.6 (d; 1H J = 14, Ph-CH=); 7.05–7.45 (m; 15H, arom); 9.5–9.65 (bs; 1H, NH); HRMS ($\text{C}_{25}\text{H}_{25}\text{N}$); found: 339.1981; calc: 339.1987 (M^+); mp: 149–151°C.

N-(5,5-Diphenyl-4-pentenyl)-3-phenylpropylamine maleate 60

Prepared according to *Method B* from: 5,5-diphenyl-4-pentenyl bromide and 3-phenylpropylamine; yield: 60%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.85 (qu; 2H J = 7.3, $-\text{CH}_2-$); 2.1 (q+qu; 4H J = 7.3, $-\text{C-CH}_2$, $-\text{CH}_2-$); 2.65 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 2.8–3.1 (m; 4H, $\text{CH}_2\text{-N-CH}_2$); 5.95 (t; 1H J = 7.3, $\text{Ph}_2\text{-C=CH-}$); 6.3 (s; 2H, mal); 7.0–7.4 (m; 15H, arom); 9.1–9.5 (bs; 1H, NH); HRMS ($\text{C}_{26}\text{H}_{29}\text{N}$); found: 355.2302; calc: 355.23; mp: 119.5–121.4°C.

N-(4,4-Diphenylbutyl)-3-phenyl-2-propenylamine maleate 65

Prepared according to *Method B* from: 4,4-diphenylbutyl bromide and 3-phenyl-2-propenylamine; yield: 60%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.9–2.2 (m; 2H, CH_2); 2.5–2.8 (m; 4H, CH_2 , $\text{CH}_2\text{-Ph}$); 2.8–3.2 (m; 4H, $\text{CH}_2\text{-N-CH}_2$); 6.0 (t; 1H J = 7.2, $\text{Ph}_2\text{-C=CH-}$); 6.15 (s; 2H, mal); 7.0–7.4 (m; 15H, arom); 9.0–9.6 (bs; 1H, NH); HRMS ($\text{C}_{25}\text{H}_{27}\text{N}$); found: 341.2105; calc: 341.2144 (M^+); mp: 140–141°C.

N-(2-Phenethyl)-3-phenylpropylamine maleate 67

Prepared according to *Method A* from: phenylacetaldehyde and 3-phenylpropylamine; yield: 70%.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.1 (qu; 2H J = 7.3, CH_2); 2.2 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 2.95–3.15 (m; 4H, $\text{CH}_2\text{-N}$, Ph-CH_2); 3.16–3.3 (m; 2H, $\text{CH}_2\text{-N}$); 6.3 (s; 2H, mal); 7.1–7.3 (m; 10H, arom); 9.2–9.6 (bs; 1H, NH); HRMS ($\text{C}_{17}\text{H}_{22}\text{N}$); found: 240.180; calc: 240.1752; mp: 163–165.1°C.

N-(3-Phenyl-2-propenyl)-4-phenylbutylamine maleate 68

Prepared according to *Method A* from: 3-phenyl-2-propenylaldehyde and 4-phenylbutylamine; yield: 80%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.6–1.9 (dqu; 4H J = 7.3, 2 x $-\text{CH}_2-$); 2.6 (t; 2H J = 7.3, $\text{CH}_2\text{-Ph}$); 3.05 (t; 2H J = 7.3, $\text{CH}_2\text{-N}$); 3.8 (d; 2H J = 8.0, $-\text{C-CH}_2\text{-N}$); 6.25 (s; 2H, mal); dt 1H J = 8.0, J = 13.3, $\text{CH}_2\text{-CH=}$); 6.65 (d; 1H J = 13.3, Ph-CH=); 7.05–7.45 (m; 10H, arom); HRMS ($\text{C}_{19}\text{H}_{23}\text{N}$); found: 265.183; calc: 265.1830; mp: 143.9–144°C.

Pharmacology

Materials

Platelets were from male rabbit (strain: New Zealand White, Enki, Someren, The Netherlands) and aortic rings from rabbit (strain: HY/CR, Charles River, France). PGI_2 stock solution of 1 mg/ml in KOH (1M) was stored at -10°C . Human α -thrombin (CLB Amsterdam, The Netherlands) was diluted in

buffer pH 7.4 (Tris 0.05M, NaCl 0.9% and PGE 6000, 0.1%) to obtain 10 NIH units/ml. Equine tendon collagen (Hormon Chemie, Munich, Germany), was used as an acid suspension containing 1 mg/ml isotonic buffer, pH = 2.8, diluted with NaCl 0.9% to give a suspension containing 100 µg/ml. Inositol 1,4,5-trisphosphate was obtained from Sigma Chemicals, saponin-white (code 44092) from BDH Chemicals, hypnorm from Solvay-Duphar, Weesp, The Netherlands. The test compounds were from laboratory stock.

Equipment

The equipment used was as follows: Sysmex-Toa model E-2500 (Toa Medical Electronics, Japan); Chronolog aggregometer (Chronolog Corporation, Havertown, PA, USA); cuvettes with stirbars (type 312, Baxter, Utrecht, The Netherlands); cannulation PVC tube (C3E Talas, Zwolle, The Netherlands); blood collection system A 1049 (NPBI, Emmencompascum, The Netherlands).

Binding studies

[³H]-Nitrendipine (0.3–0.5 nM) was displaced from guinea-pig and rat cerebral cortex membrane preparations (150–170 µg/ml) by the tested compounds according to a previously described procedure [22].

Phosphodiesterase (PDE) assay

PDE assay was performed according to the procedure described by Mannhold *et al* [36].

In vitro calcium-antagonistic and calcium entry blockade activity in isolated rabbit aortic rings

A male rabbit was killed by a blow on the head and exsanguinated. The thorax was opened and the descending aorta dissected free, and put into a Petri dish containing oxygenated Krebs (O₂ + CO₂ 5%) solution. The vessel was cleared of fat and connective tissue and then cut into 3–5-mm long rings. Each ring was placed onto stainless steel hooks, and then mounted in an organ bath, with one hook attached to the bath and the other to the tension transducer. The organ bath was previously filled with an oxygenated Krebs solution (NaCl; 118.1 mM, KCl 4.7 mM, MgSO₄·7H₂O 0.6 mM, KH₂PO₄ 1.2 mM, D-glucose 11.1 mM, NaHCO₃ 25.0 mM, CaCl₂·2H₂O 2.5 mM, pH 7.4 after bubbling with 5% CO₂ in O₂) and maintained at 37°C. The experiments started with repeating contractions (2 or 3) induced by noradrenaline bitartrate (0.3 µM), followed by relaxation induced by acetylcholine chloride (1 µM), which caused > 50% relaxation of the noradrenaline-induced contractions. Aortic rings were stimulated with either noradrenaline (1 M) or KCl (40 mM) respectively. Once the phasic and the tonic components of the contractile responses had occurred and stabilized, the preparation was washed with a fresh Krebs solution. The stimulation was repeated with the same agonist. Once the control responses had stabilized, the tissue was exposed to the antagonists usually starting at 0.1 µM, followed by 5 other concentrations of the same antagonist. Stock solutions of the test compounds in DMSO were diluted in an oxygenated Krebs solution. The reduction in contraction amplitude was determined as % control responses. Each compound was tested in 3 tissue preparations.

In vitro platelet aggregation test

Platelet-rich plasma (PRP)

Male rabbits were anaesthetized by an im injection of 0.3–0.5 ml/kg Hypnorm, containing 10 mg fluanison and 0.3 mg/ml fentanyl citrate. From one of the carotid arteries

free-flowing blood was collected in sodium citrate 2H₂O, 3.8% in distilled water (w/v). The citrated blood was centrifuged at 1 600 N/kg (160 g) for 15 min at room temperature. Platelet-poor plasma (PPP) was siphoned off after centrifugation of the citrated blood at 20 000 N/kg (2000 g) for 10 min. The platelets in the supernatant were counted with Sysmex blood cell counter and the supernatant was diluted with PPP in order to obtain PRP containing ≈ 400 000 platelets/mm³.

Preparation of gel-filtered platelets (GFP)

PRP (15 ml) prepared according to the above procedure were applied to Sepharose 2B-CL gel (200 ml) column and the platelets were eluted with a buffer (NaCl 140 mM, KCl 5.4 mM, MgCl₂·6H₂O 1 mM, glucose 5.55 mM, Tris 15.4 mM and bovine serum albumin 0.35% pH 7.4) at a low rate of ≈ 40 ml/h. GFP were counted and diluted with elution buffer to obtain GFP containing ≈ 400 000 platelets/mm³.

Preparation of washed platelets (WSP)

An aliquot of 1 µl PGI₂ (a solution of 5 µl in NaCl, 9.0 g/l) was prepared from the stock solution just before use and added to 1 ml citrated blood (see above). The blood was centrifuged at 1 600 N/kg (160 g) for 15 min at room temperature. PRP was siphoned off and centrifuged at 20 000 N/kg (2000 g) for 10 min at room temperature. The platelet pellet was resuspended in a Watson buffer (NaCl 134 mM, KCl 2.9 mM, NaHCO₃ 12 mM, Na₂HPO₄·2H₂O 0.34 mM, MgCl₂·6H₂O 1 mM, glucose 5 mM, HEPES 5 mM containing PGI₂ 5 ng/ml). The suspension was centrifuged again at 20 000 N/kg (2 000 g) for 10 min at room temperature. The platelets were resuspended in a Watson buffer in order to obtain a suspension containing 400 000 platelets/mm³.

The aggregation procedure was performed by pipetting a 0.40-ml aliquot of PRP, GFP or WSP respectively into a disposal cuvette containing CaCl₂·H₂O (20 µl, 125 M, in NaCl 0.9% aqueous solution). Test compounds dissolved in ethanol were added and the cuvette was placed into the aggregometer at 37°C. The optical density (OD) was recorded for 20 min at 609 nm.

Collagen (0.05 ml) suspension was added to PRP and WSP. Thrombin solution (0.05 ml) was added to GFP. OD was recorded for 15 min at 609 nm. The tested compounds are added at a starting dose of 10 µM in the reaction mixture and the concentrations were decreased by a factor of 2 until inhibition of < 25% was obtained. Each concentration of each compound was investigated in 2 experiments using PRP from different rabbits.

Skinned human platelets

Free-flowing blood was taken from healthy volunteers. WSP were prepared according to the procedure described above. Platelets were made semi-permeable by saponin treatment. Saponin-white 10 mg/ml was freshly suspended in Watson buffer and diluted to 130–150 µg/ml before addition to the platelet suspension.

A 40-ml aliquot of washed platelets was pipetted into a cuvette placed in an aggregometer at 37°C. After an incubation time of 2 min the OD was measured at 609 nm. The test compound solutions (0.025 ml) or solvent as a control, were added. The reaction mixture was incubated for 2 min at 37°C and 0.25 ml of IP₃, dissolved in Milli-Q quality water to a solution of 0.25 mmol/l, was added to the reaction mixture and incubated for 1 min at 37°C. Saponin (0.05 ml) was freshly suspended in a Watson buffer was added to a stock solution of 10 mg/ml, diluted to 130–150 µg/ml prior to the additions and the mixture incubated for 10 min at 37°C. During this 10 min period the OD was recorded.

Acknowledgments

The authors wish to thank GJ Sterk, H van der Goot and MQ Zhang for critical reading of the manuscript.

References

- 1 Bradig AF (1979) *Br Med Bull* 35, 227–234
- 2 Fleckenstein A (1977) *Annu Rev Pharmacol Toxicol* 17, 149–166
- 3 Cuthbert AW (1988) *Calcium in Drug Action Handb Exp Pharm* (Baker PF, ed) Springer-Verlag, Berlin, 83, 1–6
- 4 Zacharski LR (1988) *J Med* 145–177
- 5 Means AR, Rasmussen CD (1988) *Cell Calcium* 9, 313–319
- 6 Rink TJ, Smith SW, Tsien RY (1982) *FEBS Lett* 148, 21–26
- 7 Hurwitz L (1986) *Annu Rev Pharmacol Toxicol* 26, 225–258
- 8 Janis RA, Silver PJ, Triggle DJ (1987) *Advance in Drug Research* (Testa B, ed) Academic Press, NY, 16, 309–591
- 9 Klee CB, Vanaman TC (1982) *Advances in Protein Chemistry* (Anfisen CB, Edsall JT, Richard FM, eds) Academic Press, NY, 35, 213–321
- 10 Heidorn DB, Trewella J (1988) *Biochemistry* 27, 909–915
- 11 Herzeberg O, James MNC (1985) *Nature* 313, 653–659
- 12 Isomaa B, Engblom AC, Åkerman KEO (1989) *Biochem Biophys Acta* 998, 131–136
- 13 Blumenthal DK, Takio K, Edelman AM, Charbonneau H, Titani K, Walsh KA, Krebs EG (1985) *Proc Natl Acad Sci USA* 82, 3187–3191
- 14 Carafoli E (1991) *Physiol Rev* 71, 129–153
- 15 O'Callahan CM, Hosey MM (1988) *Biochemistry* 27, 6071–6077
- 16 Opie LH (1980) *Lancet* 1, 806–810
- 17 Regulla S, Schneider T, Nastainczyk V, Meyer HE, Hofmann F (1991) *EMBO J* 10, 45–49
- 18 Johnson JD, Vaghi PL, Crouch TH, Potter JD, Schwartz A (1982) *Adv Pharmacol Ther* 3, 121–138
- 19 Spedding M (1983) *Br J Pharmacol* 79, 225–231
- 20 Janis RA, Triggle DJ (1983) *J Med Chem* 26, 775–785
- 21 Mannhold R, Caldirola P, Timmerman H (1990) Poster presentation, XIth Int Sym Med Chem, Jerusalem
- 22 Caldirola P, Van der Goot H, Timmerman H (1992) *Eur J Med Chem* 27, 571–579
- 23 Moore ML (1949) *Organic Reactions* (Adams R, Bachmann WE, Blatt AH, Fieser LF, Johnson JR, Snyder, eds) J Wiley and Sons, London 5, 301–330
- 24 Gabriel S, Lauer WE (1890) *Ber Deutsch Chem Ges* 23, 87–95
- 25 Crouch MF, Lapetina EG (1990) *Environ Health Perspect* 84, 41–44
- 26 Veigl ML, Klevit RE, Sedwick WD (1989) *Pharmacol Ther* 44, 181–239
- 27 Rekker F, De Kort HM (1979) *Eur J Med Chem* 14, 479–488
- 28 Harthway DR, Aldestein RS (1979) *Proc Natl Acad Sci USA* 76, 1653–1657
- 29 Spedding M (1983) *Br J Pharmacol* 80, 485–488
- 30 Karaki H, Kubota H, Urakawa N (1979) *Eur J Pharmacol* 56, 237–245
- 31 Hughes AR, Putney JW Jr (1990) *Environ Health Perspect* 84, 141–147
- 32 Spedding M (1984) *Br J Pharmacol* 83, 211–220
- 33 Saida K, Van Breemen C (1983) *Circ Res* 52, 137–142
- 34 Zimmer M, Hofmann F (1987) *Eur J Biochem* 164, 411–420
- 35 Johnson JD (1984) *Biophys J* 45, 134–136
- 36 Mannhold R, Kramer A, Schaefer W, Schramm P (1987) *Arch Pharmacol* 320, 683–692

THE REACTIONS OF THE DISODIUM ADDUCT OF BENZOPHENONE ANIL¹

JAMES G. SMITH AND C. DOREEN VEACH

Exploratory Research Laboratory, Dow Chemical of Canada, Limited, Sarnia, Ontario

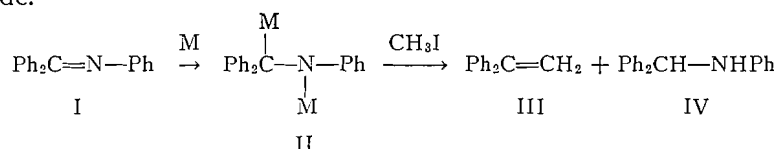
Received May 11, 1966

ABSTRACT

The disodium adduct of benzophenone anil has been treated with a variety of reagents, and the products have been isolated and identified. With alkyl halides, ethylene oxide, and diethyl sulfate, alkylation occurs at the carbon atom. With tri- and tetra-methylene dibromide, nitrogen alkylation also occurs, thereby producing substituted pyrrolidine and piperidine derivatives. Benzaldehyde abstracts the alkali metal from the adduct whereas esters react to form the *N*-acyl derivatives.

INTRODUCTION

Solutions of benzophenone anil (I) in ether solvents react with alkali metals to form a complex (II) containing two atoms of alkali metal per mole of anil (1, 2). The chemical behavior of this adduct has been examined in the past (2-4), but conflicting results have been reported. In the original study by Schlenk and Bergmann (2), benzophenone anil was the only product formed when the adduct was treated with methyl iodide or with several other reagents. On the other hand, Mikhailov (3) reported the formation of 1,1-diphenylethylene (III) and *N*-benzhydriylaniline (IV) upon treatment of II with methyl iodide.



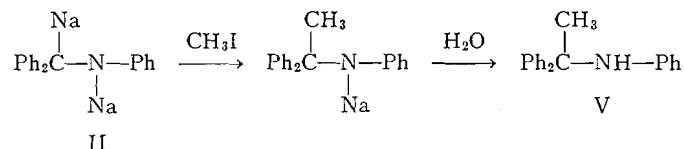
In our hands, the adduct II behaved in a manner quite different from that reported in these earlier studies. Generally speaking, the chemical behavior of the benzophenone anil adduct resembles that recently reported for the benzophenone ketyls (5-8).

Adduct Preparation

The reaction of benzophenone anil and sodium proceeds very rapidly in tetrahydrofuran. This is not surprising in view of the well-known efficacy of such solvents in the preparation of organometallic compounds. However, it is surprising that the adduct forms in diethyl ether with equal ease, especially since much longer reaction times have been employed elsewhere (2).

Reaction with Alkyl Halides

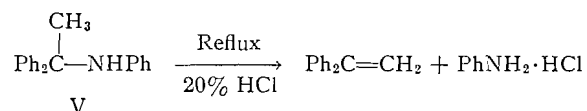
The disodium adduct II in tetrahydrofuran reacts smoothly with 1 equivalent of methyl iodide to produce the *C*-methyl derivative, *N*,1,1-triphenylethylamine (V). This behavior of the adduct was initially thought to be due to the use of tetrahydrofuran as solvent



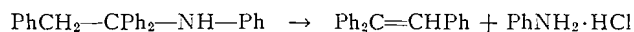
¹Contribution No. 142 from the Exploratory Research Laboratory.

rather than the diethyl ether used in the earlier investigations (2, 3). However, a repetition of the experiment with diethyl ether produced the same product accompanied by *N*-benzhydrylaniline, thus establishing that the same reaction is occurring but to a lesser extent.

The structure V of the reaction product is consistent with its nuclear magnetic resonance (n.m.r.) spectrum, and additional proof has been obtained by decomposition in 20% hydrochloric acid to 1,1-diphenylethylene and aniline.



A similar decomposition of *N*,1,1,2-tetraphenylethylamine to *N*,1,1-triphenylethylene has been reported (9).



This decomposition provides an explanation for Mikhailov's earlier observation (3) of the formation of 1,1-diphenylethylene from methyl halides and the alkali metal adducts of benzophenone anil. During his separation of the individual constituents of the crude reaction mixture, Mikhailov employed refluxing 20% hydrochloric acid. This undoubtedly resulted in decomposition of the initial reaction product to the observed unsaturated hydrocarbon. In the present experiments, the crude reaction product has also been examined by precipitating with hydrogen chloride the amines from the ether solution as their hydrochloride salts and examining the ether-soluble portion. Only small yields of 1,1-diphenylethylene have been observed.

The scope of this reaction has been investigated with a number of alkyl halides, and the results are summarized in Table I. Certain obvious trends are evident. The reaction is slow with bulky halides, such as *t*-butyl chloride, with a consequently reduced yield and the formation of *N*-benzhydrylaniline on hydrolysis. Inert halides, such as vinyl chloride, do not react whereas reactive halides, such as allyl or benzyl chloride, react rapidly, even at -60° .

The yield of product is lower with alkyl iodides than with alkyl bromides or chlorides. An investigation of the reaction products by thin-layer chromatography reveals the presence of unidentified by-products which increase in quantity when an alkyl iodide is used.

In the case of the simple alkyl halides, the products formed by nitrogen alkylation of the benzophenone anil adduct have not been isolated. However, with cyclopentyl halides, the amount of nitrogen alkylation is quite large and comparable to the carbon-alkylated product. The nitrogen-alkylated derivative VI may be isolated by decomposing the carbon-alkylated compound VII to cyclopentylidene diphenylmethane (VIII) with hydrochloric acid, leaving the nitrogen-alkylated product as the hydrochloride salt.

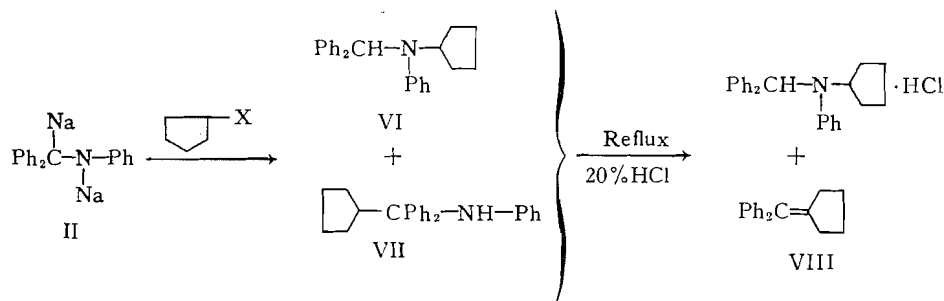


TABLE I
Reaction products with alkyl halides
$$\begin{array}{c} \text{Ph}_2\text{C}-\text{NH}-\text{Ph} \\ | \\ \text{R} \end{array}$$

Alkyl halide	R	Yield (%)	Melting point (°C)	Analysis (%)					
				Theoretical			Found		
				C	H	N	C	H	N
CH ₃ I	CH ₃	46	53-54*	87.9	7.02	5.12	87.9	7.00	5.20
C ₂ H ₅ I	C ₂ H ₅	46	67-71†	87.8	7.38	4.87	87.5	7.50	4.97
C ₃ H ₇ Cl	C ₃ H ₇	66	81-84	87.6	7.70	4.65	87.6	7.44	4.63
C ₃ H ₇ Br	C ₃ H ₇	78							
C ₃ H ₇ I	C ₃ H ₇	40							
<i>i</i> -C ₃ H ₇ Cl	(CH ₃) ₂ CH	50	113-115	87.6	7.70	4.65	87.8	7.64	4.59
<i>t</i> -C ₄ H ₉ Cl	(CH ₃) ₃ C	22	116-117	87.5	8.00	4.44	87.6	7.89	4.29
CH ₂ =CH-CH ₂ Cl	CH ₂ =CH-CH ₂	81	75-77	88.2	7.08	4.68	88.5	7.02	4.70
C ₆ H ₅ CH ₂ Cl	C ₆ H ₅ CH ₂	67, 64§	144-147‡	89.4	6.65	4.01	89.8	6.58	4.07
CH ₂ =CH-Cl	CH ₂ =CH	0	—						

*Literature (3) m.p. 50-53°.

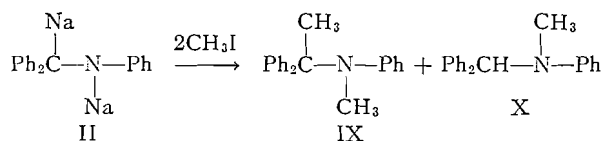
†Literature (11) m.p. 72-73°.

‡Literature (9) m.p. 143.5-144.5° and (19) 152-153°.

§Diethyl ether as reaction solvent.

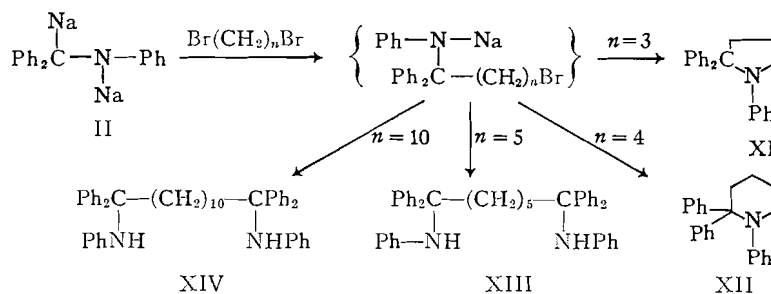
Attempts to synthesize an authentic sample of the tertiary amine VI from *N*-cyclopentylaniline and benzhydryl chloride were unsuccessful.

The reaction of the disodium adduct of benzophenone anil with 2 equivalents of methyl iodide produces a product whose n.m.r. spectrum is comparable with that expected for the dialkylated derivative, *N*-methyl-*N*,1,1-triphenylethylamine (IX). In addition to IX, a small amount of the nitrogen-alkylated derivative, *N*-methyl-*N*-benzhydrylaniline (X), can be isolated.

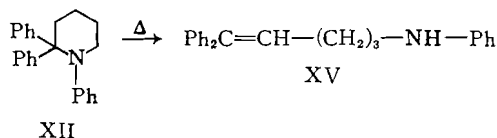


The dialkylated product IX is sufficiently stable that it can be distilled. However, attempts to purify it further by means of its hydrochloride, or by chromatography, result in it being decomposed to *N*-methylaniline and 1,1-diphenylethylene. Indeed, so facile is this decomposition that it can be effected by an equivalent amount of formic acid and the reaction followed by observation of the n.m.r. spectrum.

With polymethylene dibromides the sodium adduct of benzophenone anil reacts in two ways. Carbon alkylation presumably occurs first, and then, if the chain length of the pendant bromoalkyl group is of the proper length to bring the remaining bromo group into close proximity with the nitrogen atom, nitrogen alkylation occurs to form the heterocyclic derivative (XI or XII). However, if the chain length is too long, nitrogen alkylation is not favored and dimeric products result from the carbon alkylation of a second molecule of adduct to form the diamines (XIII or XIV).

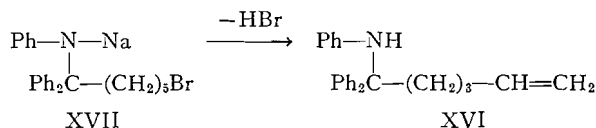


Distillation of 1,2,2-triphenylpiperidine (XII) effected its decomposition to an isomer which, on the basis of its n.m.r. spectrum, is believed to be *N*,1,1-triphenyl-5-aminopentene-1 (XV).

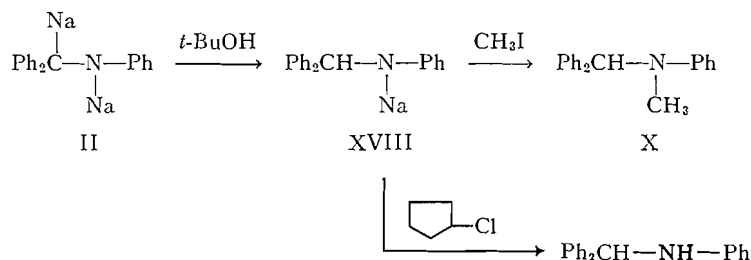


An additional product has also been isolated from the reaction leading to XIII. In this case, the material has been assigned the structure *N*,1,1-triphenyl-1-aminohexene-5

(XVI) on the basis of its n.m.r. spectrum. Its formation probably occurs by dehydrohalogenation of the intermediate XVII in a competitive side reaction.



A successful attempt has been made to take advantage of the selective reactivity of the two anionic sites in the disodium adduct of benzophenone anil by treating it first with 1 equivalent of an acid to form the amide ion XVIII, and then alkylating it with methyl iodide to produce *N*-methyl-*N*-benzhydrylaniline (X).

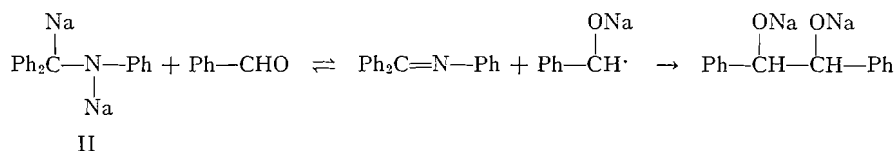


An attempt to apply this to the synthesis of *N*-cyclopentyl-*N*-benzhydrylaniline by treating XVIII with cyclopentyl chloride failed; only *N*-benzhydrylaniline was produced. It is not clear why the dianion of the disodium adduct of benzophenone anil is capable of nitrogen alkylation with cyclopentyl chloride whereas the monoanion XVIII is not.

Reaction with Benzaldehyde

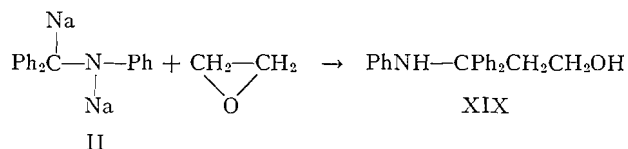
The reaction of the sodium adduct with aldehydes has been studied with benzaldehyde, an aldehyde free of enolizable (acidic) protons. The products which have been isolated are benzophenone anil and *dd, ll*-hydrobenzoin. In addition, the presence of *meso*-hydrobenzoin has been demonstrated spectroscopically.

Evidently, a transfer of the sodium from the benzophenone anil to the carbonyl group of the aldehyde occurs with regeneration of the starting material. Dimerization of the radical ion formed from the benzaldehyde produces the two diastereomeric hydrobenzoins. Similar transfers of alkali metal to carbonyl groups have been reported (6, 10).



Reactions with Ethylene Oxide

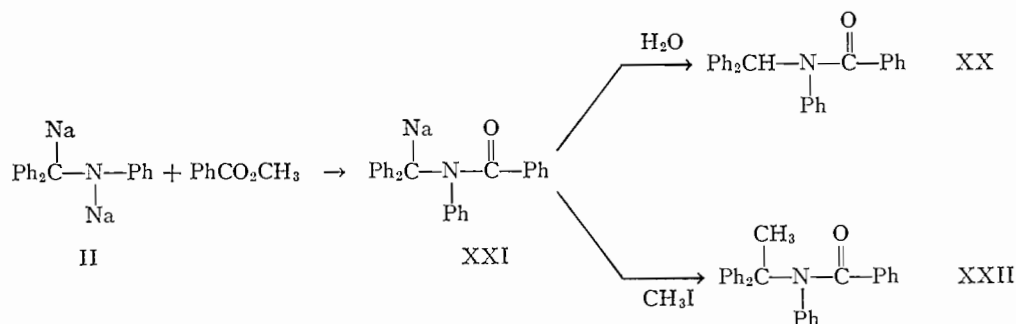
Treatment of the sodium adduct with 1 equivalent of ethylene oxide effected alkylation at the carbon atom to produce *N*,1,1-triphenyl-3-hydroxypropylamine (XIX).



Alkylation at the carbon atom is not surprising, since the anionic carbon should be more basic than the anionic nitrogen and should react faster.

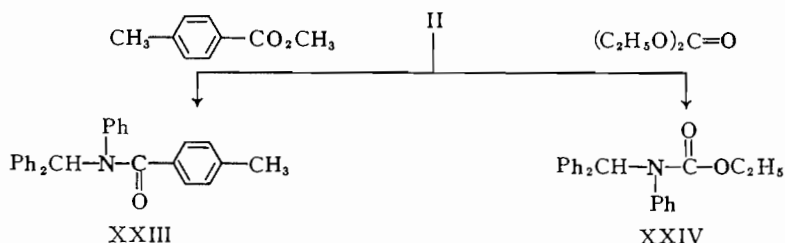
Reaction with Esters

Treatment of the disodium adduct of benzophenone anil with methyl benzoate produces *N*-benzhydrylbenzamide (XX) on hydrolysis of the initially formed reaction product XXI. That XXI is initially formed is shown by treating the intermediate with methyl iodide to produce *N*-phenyl-*N*-(1,1-diphenylethyl)benzamide (XXII).



The structure XX has been established by comparison with an authentic sample. In the infrared spectra, the amide carbonyl band appears at 1625 cm^{-1} for XX and at 1640 cm^{-1} for XXII. In the n.m.r. spectrum of XX, the benzylic proton is shifted downfield and becomes obscured by the aromatic proton band.

Similarly, methyl *p*-toluate and diethyl carbonate react with the disodium adduct II to produce the corresponding *N*-acyl derivatives XXIII and XXIV. In the latter case, the carbamate structure is indicated by the position of the carbonyl band in the infrared spectrum (1690 cm^{-1}) and by the presence of an ethyl group (from the diethyl carbonate) in the n.m.r. spectrum.



EXPERIMENTAL

Melting points are uncorrected and were determined in an open capillary with a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 221 with prism-grating interchange, using Nujol mulls of the compounds. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer, using deuterated chloroform solutions, with tetramethylsilane as an internal reference. The chemical shifts reported are in parts per million downfield from the tetramethylsilane.

Benzophenone anil was prepared from benzophenone and aniline, with aniline hydrochloride as catalyst (12). The product, after two recrystallizations from 95% ethanol, melted at $113.5\text{--}115^\circ$. It was dried under vacuum at 45° and stored in a dry box. All operations connected with the preparation and reaction of the alkali metal complexes were performed in an atmosphere of purified and dried nitrogen.

Tetrahydrofuran and diethyl ether were purified by refluxing for at least 8 h over lithium aluminium hydride and distilling onto a fresh batch of hydride for storage. When needed, the solvent was refluxed for 2 h and the required amount permitted to distill into the reaction vessel, a modified Schlenk tube (13). The tube was transferred to a dry box, where the benzophenone anil and the sodium metal (freshly cut) were weighed and added. After the tube was sealed, it was removed from the dry box and agitated in a horizontal shaker until the reaction was complete.

To study the rate of adduct formation, aliquot samples of the deep reddish purple solution were withdrawn periodically and quenched in 1:1 ethanol-water, and the alkaline mixture was titrated with 0.1 *N* standard hydrochloric acid to determine the extent of reaction. Preparative conditions were standardized at 50 ± 5 g of solvent/0.01 mole of benzophenone anil, a 100% excess of sodium, and a reaction time of 4 h, which was sufficient to ensure completion of the reaction in both tetrahydrofuran and diethyl ether.

Thin-layer chromatography was carried out using silica gel G adsorbent 0.25 mm thick, with a 10 cm rise of the solvent front. Developing solvents varied and are specified in the experimental details. The detecting spray was a 1% solution of *p*-nitrobenzenediazonium tetrafluoroborate (14) in water.

Reaction with Alkyl Halides

The solution of the adduct was transferred from the excess sodium to an oven-dried, nitrogen-filled flask equipped with a Teflon-coated magnetic stirrer bar. The solution was then cooled with a dry ice and methanol mixture and stirred, and an equivalent amount of alkyl halide was introduced by a pipette or syringe. Stirring was continued for an hour at dry-ice temperatures and then the reaction was permitted to warm to room temperature spontaneously. The final solution, generally a deep reddish brown color, was treated with 15 ml of water to destroy any remaining adduct. Extraction with ether, followed by washing, drying, and evaporating the ether extract, served to isolate the crude reaction product as an oil or gummy solid.

From this point on, the procedures differed depending on the nature of the product or the information desired. The purification procedures and additional comments together with the analytical and n.m.r. data are given below. Unless otherwise specified, each experiment was carried out with the disodium adduct prepared from 0.01 mole of benzophenone anil.

Reaction with Methyl Iodide

The reaction with methyl iodide was repeated several times because of the conflicting literature reports on the nature of the products. The roughly quantitative evaluation of the reaction products that was employed resembled that used by Mikhailov (3) but under milder conditions. The crude reaction product was dissolved in 50 ml of diethyl ether and treated with hydrogen chloride. The amine salt which precipitated out was filtered off, dried, and weighed, and the ether filtrate was evaporated and the residue weighed (1,1-diphenylethylene). The amine salt was then suspended in a mixture of 25 ml of water and 25 ml of benzene. Any aniline hydrochloride that was present dissolved in the water layer, from which it was subsequently isolated by the addition of base and ether extraction. The hydrochloride of *N*,1,1-triphenylethylamine dissociated and the free amine dissolved in the benzene layer, from which it was isolated by evaporation. The yields so obtained were 2–13% aniline, 7–19% 1,1-diphenylethylene, and 71–90% *N*,1,1-triphenylethylamine.

The identity of the isolated 1,1-diphenylethylene was confirmed by distillation and by comparison of the infrared spectrum with that of an authentic sample. The identity of the aniline was confirmed by preparing the benzenesulfonamide derivative.

The crude *N*,1,1-triphenylethylamine was obtained as a gum, and the presence of *N*-benzhydrylaniline was suspected. Small amounts could be detected by thin-layer chromatography with cyclohexane containing 17% acetic acid as developing solvent: *N*-benzhydrylaniline, R_f 0.60; *N*,1,1-triphenylethylamine, R_f 0.43. However, the amount was too small to show a benzylic proton peak in the n.m.r. spectrum of the crude amine.

The crude reaction product was purified by recrystallization from methanol (10 ml/g). The hydrochloride decomposes above 170°, forming two layers in the melting point capillary. Nuclear magnetic resonance: CH_3 singlet at 2.0 (3.0 H), NH singlet at 4.2 (1.0 H), aromatic H's complex band at 6.2–7.6 (15.8 H).

A repetition of the above experiment with diethyl ether as the solvent for adduct formation and for reaction with methyl iodide led to the formation of substantial amounts of *N*-benzhydrylaniline. The crude reaction product, isolated as previously described, contained 32% of *N*-benzhydrylaniline,² as determined by the relative areas of the appropriate n.m.r. peaks: the benzyl proton at 5.4 caused by *N*-benzhydrylaniline and the methyl protons at 2.0 caused by *N*,1,1-triphenylethylamine.

Reaction with Ethyl Iodide

The crude reaction product was dissolved in 50 ml of diethyl ether and precipitated as the hydrochloride with hydrogen chloride. The dry salt (2.535 g, 81% yield) was neutralized with aqueous sodium hydroxide, extracted with ether, concentrated, and distilled, b.p. 165–172° at 2 mm, 1.745 g (61% yield). This material crystallized and was purified for analysis by recrystallization from methanol (6 ml/g). Nuclear magnetic resonance: CH_3 triplet at 0.74 (3.0 H), CH_2 quartet at 2.53 (1.9 H), NH singlet at 4.24 (1.0 H), aromatic H's complex band at 6.2–7.6 (14.7 H).

Reaction with Propyl Halides

The crude reaction product was purified by recrystallization from methanol (6 ml/g). Nuclear magnetic resonance: CH_3CH_2 broad band at 0.7–1.5 (4.9 H) with the methyl appearing as a distorted triplet at 0.8, CH_2 triplet at 2.51 (2.0 H), NH singlet at 4.4 (1.0 H), aromatic H's complex band at 6.2–7.8 (15.0 H).

²Reference 3 reports 25–33% *N*-benzhydrylaniline formed under similar reaction conditions.

Identical experiments were carried out with propyl chloride, propyl bromide, and propyl iodide. The yield was obtained by dissolving the crude product in 10 ml of hot methanol, cooling, seeding, and allowing to crystallize for 2 days (see Table I).

The crude reaction product was also examined by thin-layer chromatography with cyclohexane containing 17% acetic acid as developing solvent. Besides the spot caused by the product (R_f 0.59), two additional spots appeared: R_f 0.63 and 0.72. These were readily seen in the product derived from propyl iodide, but not in that derived from propyl chloride. The product from propyl bromide showed an intermediate amount.

Reaction with Isopropyl Chloride

The crude product was purified by recrystallization from methanol (10 ml/g). Nuclear magnetic resonance: CH_3 doublet at 0.82 (6.0 H), CH multiplet at 2.8 (1.0 H), NH singlet at 4.3 (0.8 H), aromatic H's complex band at 6.2–7.7 (14.4 H).

*Reaction with *t*-Butyl Chloride*

The crude reaction product was chromatographed on 70 g of Woelm grade I acidic alumina using, as eluting solvents, 350 ml of hexane and then four 150 ml portions of hexane containing methylene chloride in concentrations of 5%, 10%, 25%, and 50% (v/v), respectively. Fifty milliliters of eluent was collected per fraction, and the fractions were examined by thin-layer chromatography with cyclohexane containing 17% acetic acid as developing solvent. The first two fractions contained 0.111 g of unidentified material, the next three fractions contained 0.683 g (22%) of the product *N*,1,1-triphenyl-2,2-dimethylpropylamine (R_f 0.68), and the remaining fractions (total weight 1.58 g) were mixtures of benzophenone anil (R_f 0.42), *N*-benzhydrylaniline (R_f 0.57), and product.

The product was purified by recrystallization from methanol (40 ml/g). Nuclear magnetic resonance: CH_3 singlet at 1.0 (9.0 H), NH singlet at 4.8 (0.9 H), aromatic H's complex band at 5.9–7.9 (15.2 H).

Reaction with Allyl Chloride

The crude product, *N*,1,1-triphenyl-1-aminobutene-3, was purified by recrystallization from methanol (6 ml/g). Nuclear magnetic resonance: CH_2 doublet at 3.2 (2.0 H), $-\text{CH}=\text{CH}_2$ multiplet at 4.7–5.5 (3.2 H), NH singlet at 4.4 (0.8 H), aromatic H's complex band at 6.1–7.7 (15.3 H).

Reaction with Benzyl Chloride

The crude product, *N*,1,1,2-tetraphenylethylamine, was purified by recrystallization from *n*-butanol (5 ml/g). Nuclear magnetic resonance: CH_2 singlet at 3.75 (2.1 H), NH singlet at 4.48 (0.91 H), aromatic H's complex band at 6.1–7.6 (20.0 H).

Reaction with Vinyl Chloride

No color change of the sodium adduct was noted over an 18 h period. The crude product was a viscous oil whose infrared spectrum was identical with that of *N*-benzhydrylaniline.

Reaction with Cyclopentyl Chloride

The crude reaction product was examined by thin-layer chromatography with cyclohexane containing 17% acetic acid as developing solvent. Two products were detected: R_f 0.57–0.59 and 0.67–0.68.

The crude product (5.24 g) from 0.02 mole of adduct was boiled with 30 ml of 20% hydrochloric acid for 2 h. The final mixture was treated with 30 ml of ether and filtered. The insoluble solid, which amounted to 3.21 g (44% yield), was the hydrochloride of *N*-cyclopentyl-*N*-benzhydrylaniline, m.p. 180–184°. Purification was effected by dissolving in 15 ml of warm methanol and adding 70 ml of ether to precipitate the salt. Two such treatments raised the melting point to 190–193°. Nuclear magnetic resonance: cyclopentyl protons broad band at 1.65 (8.9 H), benzyl proton at 5.8 (0.87 H), aromatic H's complex band at 6.4–7.5 (15.0 H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{26}\text{NCl}$: C, 79.2; H, 7.22; N, 3.85. Found: C, 78.7; H, 6.95; N, 3.78.

The ether layer in the filtrate from the amine hydrochloride was separated, washed, and evaporated, and the residue was distilled, b.p. 155–170° at 3 mm, to give 1.421 g of a partially crystalline liquid. A 0.50 g sample of this was recrystallized from 2 ml of methanol to give 0.20 g of cyclopentylidene diphenylmethane, m.p. 61–63°; the mixed melting point with an authentic sample was undepressed. The crude distillate was analyzed by vapor-phase chromatography, using a 7 ft long $\frac{1}{8}$ inch outside diameter column packed with 30% Apiezon on Chromosorb W heated at 248°, and using helium as carrier gas. The material was found to consist of 70% of cyclopentylidene diphenylmethane (representing a 21% yield) and 28% of an unknown material (relative retention time 1.53).

The authentic sample of cyclopentylidene diphenylmethane, m.p. 61–63°, was prepared from methyl cyclopentanecarboxylate and excess phenylmagnesium bromide followed by dehydration of the alcohol (without isolation) in refluxing acetic anhydride (15, 16). Nuclear magnetic resonance: CH_2 multiplet at 1.6 (4.0 H), CH_2 multiplet at 2.4 (4.0 H), aromatic H's singlet at 7.2 (9.8 H).

*Decomposition of *N*,1,1-Triphenylethylamine*

N,1,1-Triphenylethylamine (2.06 g, 0.076 mole) was refluxed with 10 ml of 20% hydrochloric acid for 1 h. The acid solution was extracted with 10 ml of benzene, washed twice with 5 ml of water, and dried over sodium sulfate. The dried solution was filtered and evaporated to give 1.075 g of a liquid residue. This was

distilled under vacuum, b.p. 76–82° at 2 mm, to yield 0.965 g (71%) of 1,1-diphenylethylene, whose infrared spectrum was identical with that of an authentic sample.

The aqueous acid phase and washings were combined, made alkaline, and extracted with ether. After the ether layer was washed, dried over sodium sulfate, and evaporated, a residue of 0.441 g of aniline (62%) was obtained. Its identity was established by preparing the benzenesulfonamide, m.p. 109–110°, undepressed on admixture with an authentic sample.

Reaction with 2 Equivalents of Methyl Iodide

The disodium adduct was treated with 0.02 mole of methyl iodide at –60°. Within 2 h the solution had decolorized, and thin-layer chromatography with 7:2:2 benzene – tetrahydrofuran – 98% formic acid as solvent showed the presence of four products: R_f 0.13, 0.26, 0.45, and 0.85. The first (R_f 0.13) and last (R_f 0.85), *N*-methylaniline and 1,1-diphenylethylene, respectively, were by far the largest; the other two were relatively small. One of these (R_f 0.39) is *N*-methyl-*N*-benzhydrylaniline (see below), and the other (R_f 0.26) is unknown.

The product was isolated by an ether extraction; after evaporation of the solvent, the residue (2.43 g) was distilled. Two fractions were collected: 0.746 g, b.p. 50–140° at 2 mm, and 1.225 g, b.p. 175–180° at 2 mm; 0.121 g was left as a residue. Thin-layer chromatography showed the first fraction to contain only *N*-methylaniline and 1,1-diphenylethylene, whereas the second contained these as the major components as well as the by-products, R_f 0.26 and 0.39.

The n.m.r. spectrum of this second fraction (CH_3 singlet at 1.79 (2.7 H), CH_2 singlet at 2.71 (3.0 H), aromatic H's complex band at 6.6–7.6 (16.8 H)) strongly indicated that the material was primarily *N*-methyl-*N*,1,1-triphenylethylamine. A small peak in the n.m.r. spectrum at 5.4 (equivalent to 0.2 H) was caused by an impurity, 1,1-diphenylethylene; this, in turn, affected the integration of the aromatic protons, giving too high a value. The addition of formic acid to the solution of the amine in the n.m.r. sample tube caused a marked change in the spectrum over a 24 h period. The peaks caused by the methyl groups decreased in intensity, the peak caused by the 1,1-diphenylethylene impurity grew larger, and a new peak appeared at 3.2 caused by *N*-methylaniline (in formic acid – deuterated chloroform).

N-Methyl-*N*,1,1-triphenylethylamine (0.547 g, 0.0019 mole) was dissolved in 25 ml of ether and treated with hydrogen chloride. A gum separated which crystallized when allowed to stand for 16 h. This was filtered off and weighed (0.275 g). The ether layer was evaporated to give 0.321 g (94% yield) of 1,1-diphenylethylene, whose identity was established by its infrared spectrum. The solid which was filtered off was treated with 5 ml of water containing 1 drop of concentrated hydrochloric acid and 5 ml of ether. The ether layer was separated, washed once with water, evaporated, and dried at 40° under vacuum.

The residue from the evaporation was dissolved in 5 ml of ether and treated with hydrogen chloride. A gummy solid (0.037 g) separated out and was dissolved in 1 ml of methanol; the solution was treated with 10 ml of ether, and a solid (0.020 g, m.p. 150–152.5°) precipitated out. The mixed melting point of the solid with *N*-methyl-*N*-benzhydrylaniline hydrochloride was 153–155° and its infrared spectrum was identical with that of an authentic sample.

The aqueous acid layer was made basic, extracted with ether, and evaporated to give 0.156 g (88% yield) of *N*-methylaniline, identified by comparison of its infrared spectrum with that of an authentic sample.

Reaction with 1,4-Dibromobutane

The adduct from 0.02 mole of benzophenone anil was treated with 2.38 ml (0.02 mole) of 1,4-dibromobutane at –60°. The crude orange product, isolated as previously described, amounted to 6.25 g. This was dissolved in 40 ml of *n*-hexane, and chromatographed on 60 g of Woelm grade I basic alumina packed in a 16 × 430 mm column, with 100 ml of *n*-hexane and then 100 ml of hexane – 10% benzene as eluting solvent. The color remained on the column and was not further investigated, and 5.22 g of a semisolid was recovered. This was dissolved in 60 ml of hot methanol and cooled to approximately 30 °C, and the warm solution was decanted from the gums which separated. Cooling the decantate to 10° overnight gave 2.77 g (44% yield), m.p. 74.5–77°, of 1,2,2-triphenylpiperidine.

The gum (1.35 g) crystallized when allowed to stand, and melted at 74–76.5°; the mixed melting point with the above product was 74–76.5°. The combined yield was 65%. Nuclear magnetic resonance: CH_2 broad band at 1.6 (3.95 H), CH_2 complex triplet at 2.5 (1.9 H), CH_2 complex triplet at 3.75 (1.9 H), aromatic H's complex band at 6.5–7.6 (15.0 H). The spectrum was unchanged after the solution was shaken with D_2O , indicating the absence of an amine proton.

Anal. Calcd. for $\text{C}_{23}\text{H}_{23}\text{N}$: C, 88.1; H, 7.41; N, 4.47. Found: C, 88.1; H, 7.16; N, 4.52.

At one point, an attempt was made to purify the crude product by vacuum distillation. The main fraction, b.p. 210–220° at 1 mm, was a yellow mobile liquid (the original crude material was a gum) and had an R_f (1:1 cyclohexane–chloroform) of 0.45, whereas the original material had an R_f of 0.70. Evidently some change had occurred, perhaps caused by trace amounts of acid remaining in the crude product.

This material (1.501 g) was dissolved in 25 ml of diethyl ether and treated with hydrogen chloride. The solid which precipitated (1.326 g, m.p. 175–180°) was dissolved in 10 ml of methanol; 35 ml of diethyl ether was added to give 1.115 g, m.p. 180–183°. An analytical sample was recrystallized from methanol, m.p. 182–184°. Nuclear magnetic resonance of the free amine: CH_2 quartet at 1.65, CH_2 quintet at 2.06 (combined

areas 4.0 H), CH₂ triplet at 2.96 (1.95 H), NH singlet at 3.34 (1.0 H), CH triplet at 6.00 (0.85 H), aromatic H's complex band at 6.4–7.4 (15.5 H).

Anal. Calcd. for C₂₃H₂₄ClN: C, 78.9; H, 6.92; N, 4.00. Found: C, 78.8; H, 6.71; N, 3.96.

The structure appears to be *N*,1,1-triphenyl-5-aminopentene-1.

Reaction with 1,3-Dibromopropane

The reaction of the sodium adduct and 1,3-dibromopropane was quite rapid at –60 °C. The crude product (3.265 g) was crystalline and was readily purified by recrystallization from methanol (20 ml) to give 2.24 g (75% yield) of 1,2,2-triphenylpyrrolidine, m.p. 112–114°. The analytical sample, after two additional crystallizations, had m.p. 115–116.5°. Nuclear magnetic resonance: CH₂ quintet at 1.74 (1.8 H), CH₂ triplet at 2.60 (1.85 H), CH₂ triplet at 3.70 (1.85 H), aromatic H's complex band at 6.0–7.6 (15.0 H).

Anal. Calcd. for C₂₂H₂₁N: C, 88.2; H, 7.08; N, 4.68. Found: C, 88.6; H, 7.06; N, 4.66.

Reaction with 1,5-Dibromopentane

The crude reaction product (3.35 g) was dissolved in 15 ml of hot *n*-propanol and allowed to stand for 24 h at room temperature. The product, *N,N'*,1,1,7,7-hexaphenylheptanediamine-1,7, separated slowly, 1.513 g (51% yield), m.p. 141–145°. Two recrystallizations from *n*-propanol gave an analytical sample, m.p. 154–156°. Nuclear magnetic resonance: CH₂ broad band at 1.1 (6.0 H), CH₂ broad band at 2.4 (3.8 H), NH very broad band at 4.2 (1.7 H), aromatic H's complex band at 6.2–7.7 (30.0 H).

Anal. Calcd. for C₄₃H₄₂N₂: C, 88.0; H, 7.23; N, 4.78; mol. wt. 589. Found: C, 88.3; H, 6.95; N, 4.87; mol. wt. 590.

The filtrate from the crude product was concentrated under vacuum, and the residue (1.53 g) was dissolved in 20 ml of hexane and placed on a 16 × 430 mm column of Woelm grade I basic alumina. Elution was carried out with 150 ml of hexane, 100 ml of hexane – 10% benzene, 100 ml of hexane – 25% benzene, 100 ml of hexane – 50% benzene, and finally 100 ml of benzene – 50% methylene chloride. The eluate was collected in 50 ml fractions. Fractions 1, 2, and 3 contained no material, and the remaining fractions contained 1.24 g. Examination of these by thin-layer chromatography with benzene – tetrahydrofuran – 98% formic acid (70:15:15) as developing solvent showed that fractions 4–7 (1.01 g) contained an unknown material and that fraction 9 (0.131 g) was the hexaphenylheptanediamine. The unknown material was combined and recrystallized from 25 ml of methanol, with cooling to 10°, to give 0.637 g of a solid, m.p. 55–58°. This was recrystallized again for an analytical sample, m.p. 58–59°.

Anal. Calcd. for C₂₄H₂₅N: C, 88.0; H, 7.71; N, 4.28. Found: C, 87.8; H, 7.72; N, 4.41.

On the basis of its n.m.r. spectrum, the structure was considered to be *N*,1,1-triphenyl-1-aminoheptene-5. The spectra showed a broad CH₂ band at 1.3 (2.0 H), a CH₂ quartet at 1.9 (2.2 H), a complex triplet at 2.5 (2.0 H), an NH band at 4.35 (0.85 H), two major peaks with complex fine structure at 4.7 and 4.9 caused by the vinyl group, a complex multiplet at 5.5 (total area 2.8 H), and a complex series of peaks at 6.1–7.4 (15.5 H) caused by the aromatic protons.

Reaction with 1,10-Dibromodecane

The crude reaction product from 0.01 mole of the sodium adduct in tetrahydrofuran and 1.5 g (0.005 mole) of 1,10-dibromodecane (3.751 g) was recrystallized from 25 ml of methanol and 13 ml of benzene. The recrystallized product amounted to 3.114 g (94% yield), m.p. 152–155°, of *N,N'*,1,1,12,12-hexaphenyldodecanediamine-1,12 having an orange color. Attempts to remove this color by recrystallization from *n*-butanol in the presence of Norit failed. Purification was finally effected by placing a solution of 1.65 g of the product in 30 ml of 1:1 hexane–benzene on a 16 × 450 mm column of 60 g of Woelm grade I basic alumina. Elution with 300 ml of the solvent removed 1.47 g of an almost colorless material, m.p. 147–152°; the color remained on the column. Two recrystallizations from *n*-butanol (20 ml/g) raised the melting point to 155–156.5°. Nuclear magnetic resonance: CH₂ broad band at 1.07 (8.0 H), CH₂ broad band at 2.48 (1.9 H), NH broad band at 4.26 (0.8 H), aromatic H's complex band at 6.2–7.7 (15.0 H).

Anal. Calcd. for C₄₈H₅₂N₂: C, 87.7; H, 7.99; N, 4.26; mol. wt. 657. Found: C, 88.0; H, 8.09; N, 4.15; mol. wt. 660.

Reaction with Benzaldehyde

The crude reaction product (3.41 g) was recrystallized from 20 ml of ethanol to give 0.987 g of benzophenone anil, m.p. 107–110°. A recrystallized sample of this, m.p. 110–113°, showed no depression on admixture with an authentic sample.

The filtrate from the recovered benzophenone anil was evaporated and the residue chromatographed on 70 g of Woelm grade I basic alumina packed into a 16 × 430 mm column. Elution with 250 ml of 1:1 benzene–hexane removed 1.36 g of a solid which, on recrystallization from 10 ml of hexane, gave 0.967 g, m.p. 77–80°. Investigation of this material by thin-layer chromatography with benzene as developer showed that it consisted of benzophenone anil (*R*_f 0.60) and *N*-benzhydriylaniline (*R*_f 0.73); n.m.r. analysis established that it was a mixture of 1 part of the former and 2 parts of the latter.

It was necessary to use methylene chloride plus 5% methanol and finally acetone plus 5% methanol to remove anything more from the alumina column. These eluents gave 0.701 g of a solid which, on recrystallization from 10 ml of benzene, gave 0.395 g of *dd,II*-hydrobenzoin, m.p. 113–120°, undepressed on admixture

with an authentic sample. Comparison of the infrared spectrum of the isolated material with that of an authentic sample confirmed its identity.

The solvent in the benzene filtrate from the recrystallization was evaporated and the residue was recrystallized from water to give 0.176 g of a solid, m.p. 80–85°. An examination of the infrared spectrum of this material showed it to be a mixture of *dd, ll*-hydrobenzoin and *meso*-hydrobenzoin.

The authentic sample of *meso*-hydrobenzoin was prepared by sodium borohydride reduction of benzoin in 80% dioxane. It was recrystallized from water and had m.p. 134–136.5°.

dd, ll-Hydrobenzoin was prepared by acetolysis of α -stilbene dibromide by the procedure of Breuer and Zincke (17). Two recrystallizations from 80% water – 20% ethanol gave material having m.p. 117–120°.

The total yields of isolated compounds were 50% benzophenone anil and 25% *N*-benzhydrylaniline (based on the original benzophenone anil), and 65% of the diastereomeric hydrobenzoin (based on the benzaldehyde used).

Reaction with Ethylene Oxide

The crude reaction product from 0.01 mole of adduct and 0.01 mole of ethylene oxide amounted to 3.12 g. This was crystallized from 15 ml of petroleum ether (b.p. 30–60°) to give 2.17 g (72% yield) of an orange solid, m.p. 118–122°. Recrystallization from 25 ml of hexane and 10 ml of benzene with 2 g Norit and a hot filtration sufficed to remove the color and give an analytical sample, m.p. 122–125°. Nuclear magnetic resonance: CH₂ triplet at 2.67 (1.85 H), CH₂ triplet at 3.51 (2.0 H) superimposed on a broad NHOH band at 3.3–3.7, aromatic H's complex band at 6.2–7.6 (14.5 H). The peak areas were determined after the NHOH band was eliminated with D₂O. The difference between the peak areas of the 3.5 triplet plus the NHOH band before and after D₂O treatment established that the broad NHOH band corresponded to 1.9 H.

Anal. Calcd. for C₂₁H₂₁NO: C, 83.1; H, 6.99; N, 4.62. Found: C, 83.6; H, 6.96; N, 4.57.

Reaction with Methyl Benzoate

The crude reaction product from 0.01 mole of sodium adduct and 0.01 mole of methyl benzoate was recrystallized from 10 ml of methanol to give 2.50 g (69% yield) of *N*-benzhydrylbenzanilide, m.p. 108–110°; the mixed melting point with an authentic sample was undepressed, and the infrared spectra of the material and of an authentic sample were identical.

The authentic sample was prepared by refluxing *N*-benzhydrylaniline and an equivalent amount of benzoyl chloride in pyridine for 16 h. The crude product was crystallized from hexane, and recrystallized once from hexane and once from methanol, m.p. 108–109°. Nuclear magnetic resonance: aromatic H's only in a complex band at 6.5–7.5 (the benzylic proton is shifted into the aromatic region).

Anal. Calcd. for C₂₆H₂₁NO: C, 85.9; H, 5.83; N, 3.85. Found: C, 85.7; H, 5.70; N, 3.80.

Reaction with Methyl *p*-Toluate

The crude product was purified by one crystallization from methanol and two recrystallizations from hexane to give 1.562 g of *N*-phenyl-*N*-benzhydryl-*p*-toluamide, m.p. 112.5–114° (41% yield). Nuclear magnetic resonance: CH₃ singlet at 2.15 (3.0 H), aromatic H's complex band at 6.5–7.5 (20.0 H), indicating that the 19 aromatic protons and the 1 benzyl proton are in the same region.

Anal. Calcd. for C₂₇H₂₃NO: C, 85.9; H, 6.15; N, 3.71. Found: C, 85.6; H, 5.98; N, 3.58.

Reaction with Diethyl Carbonate

Diethyl carbonate (0.01 mole) produced 3.15 g of a crude product which was chromatographed on 60 g of Woelm basic alumina grade I. Fifty milliliter fractions were collected and the solvents used were 100 ml of hexane, 100 ml of hexane – 10% benzene, 50 ml of hexane – 25% benzene, and 100 ml of hexane – 50% benzene.

This treatment removed 1.82 g of material from the column. Additional eluting solvent containing methyl-ene chloride removed the remaining material, but no products could be isolated from it.

The 1.82 g was covered with petroleum ether (b.p. 30–60°). After the mixture had stood overnight at 10°, the solution was decanted from the ethyl *N*-benzhydrylphenylcarbamate, which amounted to 1.53 g (46% yield), m.p. 54–58°. Two recrystallizations from 20 ml of petroleum ether (b.p. 30–60°), with cooling to 10°, gave 1.03 g of the carbamate, m.p. 60–62°. Nuclear magnetic resonance: CH₃ triplet at 1.1 (3.3 H), CH₂ quartet at 4.1 (2.0 H), CH singlet at 6.7 (1.0 H), aromatic H's complex band at 6.8–7.4 (15.0 H):

Anal. Calcd. for C₂₂H₂₁NO₂: C, 79.7; H, 6.35; N, 4.23. Found: C, 80.0; H, 6.01; N, 4.24.

Reaction with Diethyl Sulfate

The crude product obtained when the sodium adduct was treated with 0.01 mole of freshly distilled diethyl sulfate amounted to 2.98 g. One recrystallization from 10 ml of petroleum ether (b.p. 30–60°) gave 1.78 g (62% yield) of *N*,1,1-triphenylpropylamine, m.p. 67–70.5°.

Stepwise Reaction with Methyl Benzoate and Methyl Iodide

The sodium adduct (0.01 mole) was allowed to react with 0.01 mole of methyl benzoate for 1 h at –60° and for 4 h at room temperature. The solution was then cooled again to –60° and 0.01 mole of methyl iodide added; after the solution had warmed to room temperature, it was allowed to stand overnight.

The crude product, isolated by ether extraction, amounted to 3.47 g and was crystallized from 30 ml of *n*-hexane to give 2.39 g (63% yield) of the benzamide of *N*,1,1-triphenylethylamine, m.p. 142–144°. One recrystallization from *n*-butanol and one from isopropanol raised the melting point to 146.5–149°. Nuclear magnetic resonance: CH₃ singlet at 2.0 (2.9 H), aromatic H's complex band at 6.7–7.6 (20.0 H), very similar in structure to that of *N*-benzhydrylbenzanilide.

Anal. Calcd. for C₂₇H₂₃NO: C, 85.9; H, 6.15; N, 3.71. Found: C, 85.9; H, 6.13; N, 3.70.

Preparation of N-Methyl-N-benzhydrylaniline³

A solution of 15.0 g (0.074 mole) of benzhydryl chloride and 17.4 g (0.162 mole) of *N*-methylaniline in 50 ml of benzene was stirred at room temperature for 16 h, during which time a precipitate formed. The solution was examined by thin-layer chromatography with 7:2:2 benzene – tetrahydrofuran – 98% formic acid as solvent to follow the progress of the reaction: *N*-methylaniline, *R*_f 0.12; product, *R*_f 0.59; by-products of unknown constitution, *R*_f 0.30, 0.42, and 0.74.

The solution was washed with 10% potassium hydroxide, the benzene stripped off, and the residue distilled, collecting the main fraction, b.p. 185–205° at 4 mm, 8.50 g. This was dissolved in 100 ml of diethyl ether, and hydrogen chloride was passed briefly through the solution. The resulting precipitate amounted to 2.4 g, m.p. 152–203° (decomp.).

The filtrate from this first salt was again treated with hydrogen chloride to give 4.63 g of a second crop, m.p. 159–160°. This was dissolved in 15 ml of chloroform, the solution was filtered to remove a small amount of insoluble material, and 25 ml of ether was added. The product amounted to 4.40 g, m.p. 160–161°. Nuclear magnetic resonance: CH₃ singlet at 3.33 (2.90 H), CH singlet at 6.44 (1.02 H), aromatic H's in two broad bands at 6.9–8.7 (15.0 H); for the free amine: CH₃ singlet at 2.73 (2.95 H), CH singlet at 6.15 (0.92 H), aromatic H's complex band at 6.5–7.5 (15.0 H).

Anal. Calcd. for C₂₀H₂₀NCl: C, 77.5; H, 6.52; N, 4.52. Found: C, 77.1; H, 6.59; N, 4.35.

*Stepwise Reaction with *t*-Butyl Alcohol and Methyl Iodide*

The disodium adduct was treated at –60° with 0.94 ml (0.01 mole) of *t*-butyl alcohol. After the dark-green solution was allowed to warm to room temperature for 2 h, the solution was recooled and 0.62 ml (0.01 mole) of methyl iodide added. When warmed to room temperature, the solution changed from a dark-green color through a royal blue to a clear pale yellow. After 16 h, the solution was treated with water, and the reaction product isolated by ether extraction.

The gummy residue remaining after evaporation of the ether was dissolved in 50 ml of diethyl ether, and hydrogen chloride was bubbled through to precipitate the hydrochloride of *N*-methyl-*N*-benzhydrylaniline, 2.80 g, m.p. 146–149°. This salt was dissolved in 10 ml of methanol and the solution treated with 25 ml of ether. The solid which precipitated amounted to 2.0 g (65% yield), m.p. 160–161°, undepressed on admixture with an authentic sample. Its infrared spectrum was identical with that of the authentic sample.

*Stepwise Reaction with *t*-Butyl Alcohol and Cyclopentyl Chloride*

The above experiment was repeated with 0.01 mole of cyclopentyl chloride instead of the methyl iodide. The crude reaction product gave 2.77 g (92% yield) of the hydrochloride of *N*-benzhydrylaniline, m.p. 196–198°. Dissolution in 40 ml of methanol followed by crystallization from 60 ml of ether gave 2.17 g (72% yield) of the salt, m.p. 198–200°, undepressed on admixture with an authentic sample. Its infrared spectrum was identical with that of the authentic sample.

ACKNOWLEDGMENTS

The authors are indebted to Mr. H. Mak (Dow Chemical of Canada, Limited) for his assistance in recording and interpreting the n.m.r. spectra, and to Mr. L. E. Swim (The Dow Chemical Company, Midland, Michigan) for the microanalyses.

REFERENCES

1. W. SCHLENK, J. APPENRODT, A. MICHAEL, and A. THAL. Ber. **47**, 473 (1914).
2. W. SCHLENK and E. BERGMANN. Ann. **463**, 281 (1928).
3. B. M. MIKHAILOV and K. N. KURDYUMOVA. J. Gen. Chem. USSR Engl. Transl. **26**, 899 (1956); Zh. Obshch. Khim. **26**, 786 (1956).
4. A. MATHIAS and E. WARHURST. Trans. Faraday Soc. **58**, 942 (1962).
5. E. L. ANDERSON and J. E. CASEY, JR. J. Org. Chem. **30**, 3959 (1965).
6. S. SELMAN and J. F. EASTHAM. J. Org. Chem. **30**, 3804 (1965).
7. D. V. IOFFE. Chem. Abstr. **63**, 17953g (1965); Biol. Aktivn. Soedin. Akad. Nauk SSSR, 147 (1965).
8. P. J. HAMRICK, JR. and C. R. HAUSER. J. Am. Chem. Soc. **81**, 493 (1959).
9. R. C. FUSON, R. J. LOKKEN, and R. L. PEDROTTI. J. Am. Chem. Soc. **78**, 6064 (1956).
10. A. G. BROOK, H. L. COHEN, and G. F. WRIGHT. J. Org. Chem. **18**, 447 (1953).
11. H. GILMAN, A. H. HAUBEIN, G. O'DONNELL, and L. A. WOODS. J. Am. Chem. Soc. **67**, 922 (1945).

³This procedure follows that used by Cromwell and Fitzgibbon (18) for similar compounds.

12. G. REDDELIEN. Ber. **46**, 2718 (1913).
13. J. W. B. REESOR, J. G. SMITH, and G. F. WRIGHT. J. Org. Chem. **19**, 940 (1954).
14. N. D. CHERONIS and J. B. ENRIKIN. Semimicro qualitative organic analysis. 2nd ed. Interscience Publishers, Inc., New York. 1957. pp. 237 and 730.
15. S. S. NAMETKIN and M. A. VOLODINA. J. Gen. Chem. USSR Engl. Transl. **18**, 2033 (1948); Chem. Abstr. **43**, 3797a (1949).
16. G. EGLOFF. Physical constants of hydrocarbons. Vol. III. Reinhold Publishing Corp., New York. 1946. p. 456.
17. A. BREUER and T. ZINCKE. Ann. **198**, 154 (1879).
18. N. H. CROMWELL and W. E. FITZGIBBON. J. Am. Chem. Soc. **70**, 387 (1948).
19. T. W. J. TAYLOR, J. S. OWEN, and D. WHITTAKER. J. Chem. Soc. 206 (1938).