Synthesis and Pharmacology of *trans*-4-*n*-Propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-7- and -9-ols: The Significance of Nitrogen pK_a Values for Central Dopamine Receptor Activation

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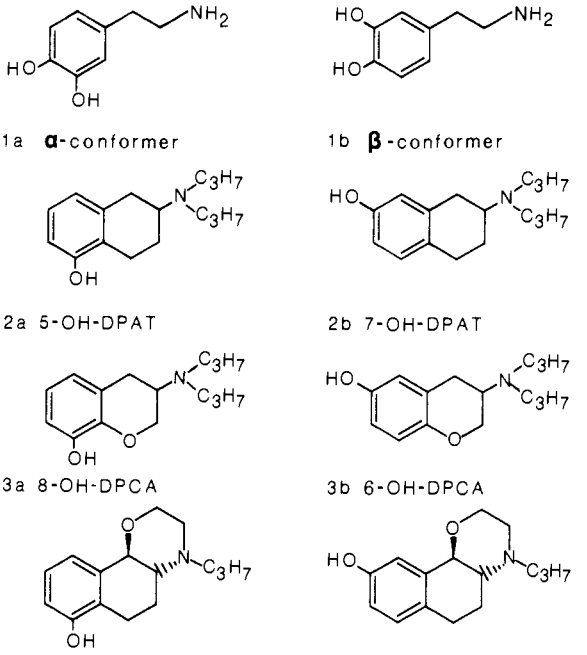
The 6-oxa analogues of potent dopamine agonists, hexahydronaphthoxazines (**4a**, **4b**), have been tested for dopamine receptor binding and stimulating activity and were found to be almost inactive. pK_a value determinations indicated that these compounds are protonated to ~2%, while potent compounds are protonated to a much greater extent. These results strongly support the assumption that the protonated form of DA agonists is the active species at the receptor.

Several reviews outlining the structural requirements for agonist activity at dopamine receptors have been published.[1-3] Current models of both the D_1 and D_2 receptor are based on a model proposed by McDermed et al.[4] and Tedesco et al.,[5] who studied the dopaminergic activity of some 2-aminotetralins. The main features of this model include binding sites for the basic nitrogen and the *m*-hydroxyl group of the 2-aminotetralins and a zone of steric intolerance. In the literature there is a controversy about the role of the nitrogen atom at the receptor. It has been proposed that the basicity of the amine is a critical factor in activating the receptor.[6] Some studies indicate that an uncharged nitrogen atom is required for binding,[7,8] while others have reported that a charged form of the nitrogen atom is a prerequisite for activity.[1,9] Nichols[10] has suggested that the real importance of this atom lies in the orientation of its unshared electron pair, whether free or protonated. An optimum receptor interaction might be dependent on the orientation of the unshared pair. Despite all these suggestions, the nitrogen atom will exist mainly in the protonated form at physiological pH. The most direct evidence for the suggestion that the charged form of the nitrogen atom is of importance comes from the work of Miller et al.,[11,12] who have prepared the dimethylsulfonium analogues of dopamine and ADTN and have shown that these compounds possess D_2 receptor agonistic activities.

Cannon has defined α- and β-conformers of dopamine (**1a**,**b**), in which the catechol ring is coplanar with the plane of the ethylamine side chain, and he proposed that these conformations are significant in DA agonist receptor interactions. Results from various groups[13-15] working with semirigid analogues of DA, such as the 2-aminotetralins, have shown that phenolic groups at the 5- and 7-positions yield analogues with high dopaminergic activity. In addition a *N*,*N*-dipropyl substituent pattern has also been found to provide maximum potency (**2a**,**b**). It has been shown that isosteric replacement of the methylene group at C4 in the 2-aminotetralins by an oxygen atom yields the 3-chromanamine **3a**, which is also a potent DA agonist.[16]



Encouraged by the interesting pharmacological profile of the *trans*-hexahydronaphthoxazines **4a**,**b**[17,18] and 3-

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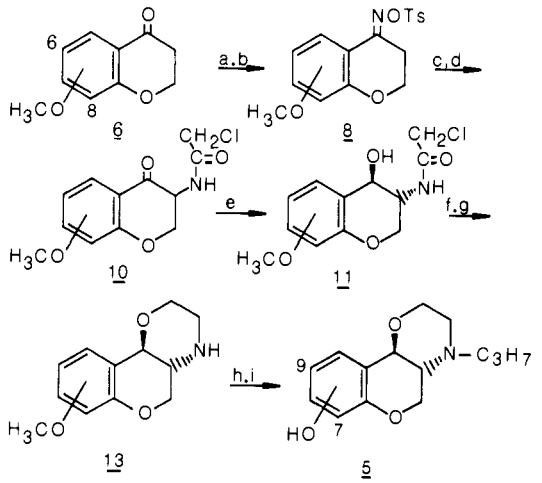
0022-2623/88/1831-2178$01.50/0

Scheme I[a]



[a] Reagents: (a) NH_2OH; (b) TsCl; (c) NaOEt, HCl, H_2O; (d) $ClCH_2COCl$; (e) $NaBH_4$; (f) NaOH; (g) $LiAlH_4$; (h) C_3H_7I; (i) BBr_3.

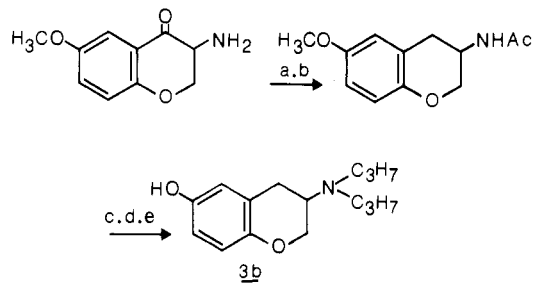
(dipropylamino)-3,4-dihydro-2*H*-1-benzopyran-8-ol (**3a**)[16] we have combined elements of the structures of **3** and **4** and have prepared the 6-oxa analogues of **4**, i.e. the *trans*-4-*n*-propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-7- and 9-ols (PTBO, **5a**,**b**). These particular compounds were chosen because an inspection of molecular models of the *trans*-octahydrobenzo[*f*]-quinolines and the *trans*-hexahydronaphthoxazines and the title compounds reveals a close similarity in shape and size, as well as a locational correspondence between the hydroxyl and amine functions. To complete the series, the β-conformer 3-(dipropylamino)-3,4-dihydro-2*H*-1-benzopyran-6-ol (**3b**) was also prepared.

Because lipophilicity has an important effect on dopaminergic potency, log *P* values for these compounds were determined. In addition, due to the possible influence of the isosteric change on the basicity of the nitrogen atom, pK_a values were also determined. The in vivo dopaminergic activity of the compounds was evaluated by studying their effects on the stereotypy of rats and also for their effect on DA metabolism. Their in vitro activities were evaluated by examining their ability to displace [^{3}H]-DP-5,6-ADTN and [^{3}H]-N-0437 binding to striatal (rat, calf) tissue.

Chemistry

The synthesis of the 1-benzopyrano-1,4-oxazines **5** is outlined in Scheme I. We started with the known 4-chromanones **6**, which were readily converted into the tosyloximes **8**. Neber rearrangement of **8** with sodium ethoxide afforded the desired amino ketone **9**, which was isolated as the hydrochloride, in good yields. The free base, however, decomposed immediately on liberation from its salt. Without purification, the amino ketones were acylated with chloroacetyl chloride. When **10** was reduced with sodium borohydride, a two-component mixture **11** was obtained. The mixture was readily separated by medium-pressure chromatography with hexane-ethyl acetate (1:1) as eluent. The compound with the lower R_f value, obtained in 75% yield, was the trans component (J = 8 Hz, diaxial protons). The faster moving component (25%) was the *cis*-chloroacetamide (J = 3 Hz). The cyclization of the chloroacetamide **11** by means of 50% NaOH in 2-propanol at room temperature gave satisfactory yields of the cyclized derivative **12**, which in turn was reduced with $LiAlH_4$ to the oxazine **13**. Alkylation of the amine with propyl iodide in DMF afforded the tertiary amine **14**. Cleavage of the methoxy group in **14** was achieved without significantly affecting the two other ether functions in the molecule by use of BBr_3, at a low temperature. 3-(Dipropylamino)-3,4-dihydro-2*H*-1-benzopyran-6-ol (**3b**) was readily prepared from one of the intermediates in the synthesis of **5** (Scheme II) according to a modification of the method described by Horn et al.[16]

Scheme II[a]



[a] Reagents: (a) Ac_2O; (b) H_2, Pd–C; (c) HCl; (d) C_2H_5COOH, $NaBH_4$; (e) BBr_3.

Table I. Potency of Various Dopamine Agonists To Displace the Specific in Vitro Binding of [^{3}H]-DP-5,6-ADTN to Rat Striatal Membranes and [^{3}H]-N-0437 to Calf Striatal Membranes[a]

	in vitro binding: IC_{50}, nM			in vitro binding: IC_{50}, nM	
compd	[^{3}H]DP-5,6-ADTN	[^{3}H]N-0437	compd	[^{3}H]DP-5,6-ADTN	[^{3}H]N-0437
2a	4	16	**4a**	75	24
2b	30	63	**4b**	3	13
3a	4	8	**5a**	2923	8900
3b	180	1400	**5b**	3070	1600

[a] Each drug was assayed in triplicate over the concentration range of 10^{-11}–10^{-4} M. For further details, see Mulder et al.[19] and Van der Weide et al.[20]

Table II. In Vivo Effects of Various Dopamine Receptor Agonists on the Concentration of the Dopamine Metabolites DOPAC and HVA in Rat Striatum and on the Induction of Stereotypy

compd	dose,[a] μmol kg^{-1}	rat brain concentrations ± SEM (% of control) DOPAC	HVA	stereotypy[b] ED_{50}
2a[c]	1.0	73 ± 4.2	60 ± 1.2	
2b[c]	1.0	72 ± 3.0	56 ± 7.1	
4a[d]	0.4	101 ± 5.7	86 ± 7.0	7.5
4b[d]	0.4	67 ± 2.7	44 ± 1.9	0.5
5a	10.0	108 ± 9.5	110 ± 10.6	I[e]
5b	10.0	100 ± 13.0	100 ± 12.5	I
APO[c,d]	10.0	48 ± 1.5	40 ± 1.8	2.3

[a] Compounds were administered ip 1 h before killing. [b] The ED_{50} value for stereotypy is the dose (μmol kg^{-1}) needed to induce a continuous sniffing behavior in rats, corresponding to a score of 2 according Costall et al.[21] [c] Values taken from ref 25. [d] Values taken from ref 18. [e] I = inactive.

Results and Discussion

Dopaminergic receptor binding activity was assessed in vitro by determining each compound's IC_{50} (nM) for displacement of [^{3}H]-DP-5,6-ADTN[19] and [^{3}H]-N-0437,[20]

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Table III. Partition Coefficients (log P) and Ionization Constants (pK_a) for Various Dopamine Agonists[a]

compd	log P oct–buffer, pH 7.4	pK_{a1} (N)	pK_{a2} (OH)
2a	1.53	9.4	10.9
2b	1.45	9.4	10.7
3a	2.44	8.2	9.9
3b	2.39	8.1	9.6
4a	2.22	7.4	10.5
4b	2.09	7.5	10.9
5a	1.93	5.8	10.2
5b	1.97	6.1	10.3

[a] The pK_a values were determined according to the method of Albert and Serjeant.[22] The values are the mean of three to four determinations.

both of which are a measure of D_2 receptor binding activity. The results are summarized in Table I. As can be seen from the table, the 1-benzopyranooxazines exhibited a very weak D_2 binding activity. Determination of brain striatal HVA and DOPAC decreases, both of which reflect presynaptic dopamine activity,[15] and the induction of stereotypy, which is an indication of postsynaptic dopaminergic actions,[21] were used as in vivo models. For compounds **5a** and **5b** there was no decrease of striatal HVA and DOPAC, and both compounds were also incapable of inducing stereotypy even at doses up to 40 μmol/kg (Table II).

The very weak activity of **5a,b** compared with that of the aminotetralins **2**, chromanamines **3**, and naphthoxazines **4** cannot readily be explained simply on the basis of geometry. An inspection of the molecular models of the chromanamines **3**, the *trans*-naphthoxazines **4**, and the *trans*-1-benzopyranooxazines **5** reveals a close similarity in size and shape as well as locational correspondence between the hydroxyl and amino functions. In order to investigate the effect of the introduction of one or two oxygen atoms on the physicochemical properties of the compounds, we have determined the partition coefficients (log P) and ionizations constants (pK_a) of the compounds (Table III). From the data of Table III, all compounds appear sufficiently lipophilic to pass the blood–brain barrier. However, introduction of one or two oxygen atoms has a pronounced effect on the ionization constants of the compounds. In comparison to the 2-aminotetralins, the pK_a values decrease by 1.2 units for the chromamines **3**, 2.0 units for the naphthoxazines **4**, and as much as 3.4 units for the 1-benzopyranooxazines **5**. The pK_{a2} values in this series remain constant. On comparison with simplier molecules, such as the methoxyl derivatives of **4** and **5**, it seems reasonable to conclude that the lower pK_a values can be attributed to the NH^+ group and the higher pK_a to the phenolic OH. One can also infer from these results that the aminotetralins, chromanamines, and naphthoxazines exist to an extent of 99%, 97%, and 50%, respectively, in the protonated from at physiological pH. In contrast the 1-benzopyranooxazines are only 2–4% in the protonated form at this pH.

Since the 1-benzopyranooxazines described in this paper contain a fully extended phenylethylamine moiety analogous to that found in the aminotetralins, *trans*-octahydrobenzo[*f*]quinolines and naphthoxazines, it seemed appropriate to expect similar structure–activity relationships and it is also likely they will fit the DA receptor models of McDermed[4,5] and Wikström.[22] We therefore conclude that the unexpectedly low activity of **5a,b** is a consequence of the low pK_a values.

This work supports the conclusions reported by Miller, Uretsky, and co-workers[11,12] who have shown that the nitrogen atom in dopamine agonists can be replaced by a charged sulfur atom, indicating that it is the charged species that interacts with the active site of the receptor. This general conclusion is also in agreement with suggestions made by Seeman and Guan[9] based on [^{3}H]-SCH23390/apomorphine and [^{3}H]spiperone/apomorphine competition experiments at different pH values. Their results suggest that the charged form of apomorphine is the more active species at D_1 and D_2 receptors. It would appear that a negative charge on the receptor surface is important for the interaction between the receptor and the agonist. This may be an ionic interaction between the protonated amine and a carboxylate group of an amino acid.

Experimental Section

Melting points were determined with an Electrothermal digital melting apparatus and are uncorrected. Infrared spectra were recorded on a JASCO A-100 spectrophotometer, and only the important absorptions are given. The 60-MHz ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 B spectrometer. Chemical shifts are denoted in ppm relative to tetramethylsilane as internal standard. Splitting patterns are designated s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained with a Finnegan 3300 system. Elemental analyses were performed in the Department of Chemistry, University of Groningen. Where elemental analyses are indicated, results obtained were within 0.4% of theoretical values.

3-(Chloroacetamido)-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one (10a). To a stirred solution of sodium bicarbonate (4 g) in water (50 mL) layered with ethyl acetate (200 mL) was added 3-amino-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one hydrochloride (4.0, 17.4 mmol).[16] After the solid had dissolved, chloroacetyl chloride (1.6 mL, 17.4 mmol) was added dropwise over a period of 10 min. After the mixture was stirred at ambient temperature for 1 h, the ethyl acetate layer was separated. The aqueous layer was extracted once with ethyl acetate (50 mL). The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated to a small volume whereupon colorless crystals formed. Recrystallization from ethyl acetate gave (2.8 g, 59.6%) of 3-(chloroacetamido)-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one: mp 175^8–176^4 °C; IR (KBr) 3225 cm^{-1} (N—H), 1690 (C=O), 1655 (CONH); NMR ($CDCl_3$) δ 3.8 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Cl); MS (CI with NH_3), m/e 270 (M + 1), 287 (M + 18). Anal. ($C_{12}H_{12}NO_4Cl$) C, H, N, Cl.

3-(Chloroacetamido)-6-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one (10b). The 6-methoxy chloroacetamide **10b** was prepared by exactly the same procedure as described for the preparation of the 8-methoxy analogue. The yield of **10b** was 68%, and the pure material had the following properties: mp 154–155 °C; IR (KBr) 3275 cm^{-1} (NH), 1690 (C=O), 1655 (CONH); NMR ($CDCl_3$) δ 3.7 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Cl), 4.8 (m, 2 H, 2-CH_2), 6.9–7.4 (m, 4 H, ArH, NH); MS (CI with NH_3) m/e 270 (M + 1). Anal. ($C_{12}H_{12}NO_4Cl$) C, H, N, Cl.

***trans*-3-(Chloroacetamido)-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-ol (11a).** To a solution of 1 g (3.7 mmol) of **10a** in ethanol (25 mL) and dichloromethane (10 mL) was added sodium borohydride (200 mg) in portions. After 1 h several drops of acetic acid were added to destroy excess sodium borohydride. The mixture was poured into water (100 mL), and the product was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with water and dried ($MgSO_4$). The resulting mixture (800 mg) after solvent removal was shown to contain two components (TLC). The major one, constituting 74% of the

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mixture by GLC examination, was the desired compound, the other compound being the cis isomer. These isomers were separated cleanly by medium-pressure chromatography (ethyl acetate-hexane 1:1). Fractions were collected and concentrated in vacuo to give 225 mg (22.3%) of the cis compound and 700 mg (69.4%) of the trans compound and **11a**: mp 128–129 °C; IR (KBr) 3300 cm^{-1} (OH), 1665 (C=O); 1040 (C=O); NMR ($CDCl_3$) δ 3.7 (s, 3 H, OCH_3), 3.9 (s, 2 H, CH_2Cl), 3.9–4.6 (m, 5 H, 2-CH_2, OH, 3-CH_{ax} and 4-CH_{ax}), 6.6–7.2 (m, 4 H, ArH, NH); MS (NICI with OH^-), *m/e* 270 (M – 1). Anal. ($C_{12}H_{14}NO_4$) C, H, N.

***trans*-3-(Chloroacetamido)-6-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-ol (11b).** The chloroacetamide **11b** was prepared from **10b** according to the method used for the preparation of **11a**. Medium-pressure chromatographic separation with ethyl acetate–hexane (1:1) as eluent yielded pure *trans*-**11b** (72.4%) and *cis*-**11b** (15%). *trans*-**11b**: mp 129–130 °C; IR (KBr) 3225 cm^{-1} (OH), 1670 (C=O); NMR ($CDCl_3$) δ 3.7 (s, 3 H, OCH_3), 4.0 (s, 2 H, CH_2Cl), 3.9–4.7 (m, 5 H, OH, 2-CH_2, 3-CH, 4-CH), 6.8 (m, 3 H, ArH), 7.2 (br, 1 H, NH); MS (CI + NH_3), *m/e* 272 (M + 1). Anal. ($C_{12}H_{14}NO_4Cl$) C, H, N.

***trans*-7-Methoxy-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-3-one (12a).** To a solution of 3.2 g (11.8 mmol) of the *trans*-chloroacetamide **11a** in 150 mL of 2-propanol was added dropwise a solution of 1.0 g of NaOH in 2.0 mL of water at room temperature. The mixture was stirred 3 h before being neutralized with 10% HCl. The solvents were evaporated as much as possible, and the resulting residue was slurried in 100 mL of water and extracted with dichloromethane (4 × 25 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, and then concentrated to dryness. Recrystallization from acetone–hexane gave **12a** as white crystals: 2.9 g (72.2%); mp 232–234 °C; IR (KBr) 3175 cm^{-1} (NH), 1670 (C=O); NMR (DMSO-d_6) δ 3.8 (s, 3 H, OCH_3), 3.9–4.5 (m, 3 H, 4a-CH, 5-CH_2), 4.2 (s, 2 H, 2-CH_2) 4.7 (d, J = 8.5 Hz, 1 H, 10b-CH), 6.8 (m, 3 H, ArH), 8.3 (s, 1 H, NH); MS (CI with NH_3), *m/e* 236 (M + 1). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

***trans*-9-Methoxy-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-3-one (12b).** The chloroacetamide **11b** was converted to the lactam **12b** as described above for **12a**. Recrystallization from acetone–hexane gave pure **12b** (66.0%): mp 249–251 °C; IR (KBr) 3160 cm^{-1} (NH), 1675 (C=O); NMR (DMSO-d_6) δ 3.8 (s, 3 H, OCH_3), 3.9-4.4 (m, 3 H, 4a-CH, 5-CH_2), 4.2 (s, 2 H, 2-CH_2), 4.6 (d, 1 H, 10b-CH_{ax}), 6.8 (m, 3 H, ArH), 8.3 (br, 1 H, NH); MS (CI with NH_3), *m/e* 236 (M + 1). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

***trans*-7-Methoxy-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazine Hydrochloride (13a).** A solution of 0.5 g (2.1 mmol) of the *trans*-lactam **12a** in THF (60 mL) was added to a stirred solution of 0.2 g (5.3 mmol) of $LiAlH_4$ in 10 mL of THF cooled at 5 °C. The reaction mixture was allowed to warm to room temperature and then heated at reflux for 1 h. After cooling, excess hydride was destroyed by the careful addition of 0.2 mL of water followed by 0.2 mL of 4 N sodium hydroxide and a further 0.6 mL of water. The mixture was filtered and the solid washed with ether. The organic solvents were dried over magnesium sulfate and then evaporated under reduced pressure. The resulting oil was dissolved in dry ether, and ether saturated with gaseous HCl was added slowly to produce the oxazine hydrochloride **13a** as a white solid. Recrystallization from ethanol yielded 0.42 g (76.6%) of white crystals: mp 225–227 °C; IR (free base) 3300 cm^{-1} (NH); NMR ($CDCl_3$) free base, δ 2.1 (br, 1 H, NH), 3.7 (s, 3 H, OCH_3), 4.3 (d, J = 8 Hz, 1 H, 10b-CH_{ax}), 6.9 (m, 3 H, ArH); MS (CI with NH_3), *m/e* 222 (M + 1). Anal. ($C_{12}H_{16}NO_3Cl$) C, H, N, Cl.

***trans*-9-Methoxy-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazine Hydrochloride (13b).** Reduction of the lactam **12b** with $LiAlH_4$ as described above for **13a** gave the desired amine. Conversion to the HCl salt and recrystallization from ethanol gave 79.9% yield of **13b**: mp 260 °C dec; IR, free base, 3250 cm^{-1} (NH); NMR ($CDCl_3$), free base, δ 1.8 (br, 1 H, NH), 2.7–3.3 (m, 4 H, 2-CH_2), 3.7 (s, 3 H, OCH_3), 3.7–4.2 (m, 3 H, 4a-CH, 5-CH_2), 4.3 (d, J = 8 Hz, 1 H, 10b-CH), 6.8 (m, 3 H, ArH); MS (CI with NH_3), *m/e* 222 (M + 1). Anal. ($C_{12}H_{16}NO_3Cl$) C, H, N, Cl.

***trans*-7-Methoxy-4-*n*-propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazine Hydrochloride (14a).** Anhydrous potassium carbonate (0.45 g, 3.3 mmol) and 1 mL (1.74 g, 10.2 mmol) of propyl iodide were added to a solution of 0.26 g (1.0 mmol) of the amine HCl **13a** in 30 mL of DMF. The mixture was stirred for 5 h at 55 °C and then poured into 100 mL of water and extracted with ether (5 × 35 mL). The combined organic layer was washed with brine (5 × 10 mL) and once with a 10% ammonium chloride solution (10 mL). The ether layer was then dried over magnesium sulfate and evaporated to dryness. The resulting oil was converted to the HCl salt of the amine. The yield after crystallization from ethanol was 0.28 g (92.6%): mp 199–200 °C; IR (KBr) 2450 cm^{-1} (NH^+), 1590 (Ar); NMR ($CDCl_3$), free base, δ 0.9 (t, 3 H, 3′-CH_2), 2.1–3.0 (m, 6 H, 2-CH_2, 3-CH_2, 1′-CH_2), 3.8 (s, 3 H, OCH_3), 3.7–4.2 (m, 3 H, 4a-CH, 5-CH_2), 4.5 (d, J = 9 Hz, 1 H, 10b-CH), 6.6–7.1 (m, 3 H, ArH); MS (CI with NH_3), 264 (M + 1). Anal. ($C_{15}H_{21}ClNO_2 \cdot 0.2H_2O$) C, H, N, Cl.

***trans*-9-Methoxy-4-*n*-propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazine Hydrochloride (14b).** The reaction was carried out as described above for **14a**. Conversion to the HCl salt and recrystallization from ethanol gave pure **14b** (83.6%): mp >217 °C dec; IR (KBr) 2470 cm^{-1} (NH^+), 1610 (Ar); NMR ($CDCl_3$), free base, δ 0.8 (t, 3 H, 3′-CH_3), 1.5 (m, 2 H, 2′-CH_2), 2.0–3.0 (m, 6 H, 2-CH_2, 1′-CH_2), 3.7 (s, 3 H, OCH_3), 3.7–4.7 (m, 4 H, 4a-CH, 5-CH_2, 10b-CH), 6.8 (m, 3 H, ArH); MS (CI with NH_3), *m/e* 264 (M + 1). Anal. ($C_{15}H_{21}ClNO_2$) C, H, N, Cl.

***trans*-4-*n*-Propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-9-ol Hydrochloride (5b).** Amine HCl **14b** (0.20 g, 0.70 mmol) was dissolved in 25 mL of dichloromethane, and the temperature of the solution was lowered to –60 °C. A 0.25 M solution (5 mL) of boron tribromide in dichloromethane was then added. The reaction mixture was initially stirred for 2 h at a temperature between –30 and –40 °C and was then allowed to rise to room temperature and the reaction was stirred for a further 20 h. The reaction mixture was poured into water (100 mL) and made alkaline by the addition of ammonia. The separated aqueous layer was extracted with ether (4 × 30 mL). The combined organic extracts were washed with saturated saline (3 × 10 mL) and dried over magnesium sulfate. Removal of the solvents under reduced pressure yielded an oil. Conversion to the HCl salt and recrystallization from ethanol-ether yielded 0.14 g (73%) of pure product: mp >220 °C dec; IR (KBr) 3250 cm^{-1} (OH), 2500 (NH_3^+); NMR ($CDCl_3$), free base, δ 0.9 (t, 3 H, 3′-CH_3), 1.5 (m, 4 H), 2.6 (m, 4 H), 3.9–4.6 (m, 4 H, 4a-CH, 5-CH_2, 10b-CH), 6.2 (s, 1 H, OH), 6.7 (s, 3 H, ArH); MS (CI + NH_3), *m/e* 250 (M + 1). Anal. ($C_{14}H_{20}NO_3Cl \cdot 0.2H_2O$) C, H, N, Cl.

***trans*-4-*n*-Propyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]-1,4-oxazin-7-ol Hydrochloride (5a).** By use of the procedure used for the phenol **5b**, the 7-methoxy derivative gave the phenol **5a** in a 67% yield after recrystallization from ethanol–ether: mp 144–145 °C; IR (KBr) 3200 cm^{-1} (OH), 2525 (NH_3^+); NMR ($CDCl_3$), free base, δ, 0.9 (t, 3 H, 3′-CH_3), 1.5 (m, 4 H), 2.5 (m, 4 H); MS (CI + NH_3), *m/e* 250 (M + 1). Anal. ($C_{14}H_{20}NO_3Cl$) C, H, N, Cl.

6-Methoxy-3-(dipropylamino)-3,4-dihydro-2*H*-1-benzopyran Hydrochloride (15). Propionic acid (15.0 g, 203 mmol) was dissolved in 250 mL of dry toluene under an atmosphere of nitrogen. Sodium borohydride (2.4 g, 63 mmol) was then added and the mixture was stirred until the evolution of hydrogen had ceased. 6-Methoxy-3-chromanamine hydrochloride[24] (1.15 g, 5.3 mmol) was added and the solution was kept at 80 °C for 15 h. After cooling, the reaction mixture was poured into 200 mL of water. The separated organic layer was washed with 2 N NaOH (4 × 50 mL) and with a saturated solution of NaCl. After drying over magnesium sulfate and removal of the solvent, the resulting oil was submitted to column chromatography with ethyl acetate–petroleum ether (40–60 °C) (1:2) as the eluent. Conversion of the resulting colorless oil into the HCl salt yielded 1.24 g (77.6%) of **15** as a white solid: mp 122–124 °C; IR (KBr) 2250 cm^{-1} (NH^+); NMR ($CDCl_3$), free base, δ 0.9 (t, 6 H, 3′-CH_3), 1.5 (m, 4 H, 2′-CH_2), 2.5 (t, 4 H, 1′-CH_2), 2.8–3.5 (m, 3 H), 3.8 (s, 3 H, OCH_3), 3.8–4.4

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(m, 3 H), 6.6-6.9 (m, 3 H, ArH); MS (CI + NH_3), m/e 264 (M + 1). Anal. ($C_{16}H_{26}NO_2Cl$) C, H, N, Cl.

3-(Dipropylamino)-3,4-dihydro-2*H*-1-benzopyran-6-ol Hydrochloride (3b). The 6-methoxychromanamine **15** was O-demethylated by use of boron tribromide in dichloromethane as described for **5b**. Conversion to the HCl salt and recrystallization from ethanol-ether gave pure **16** (yield 70.8%): mp 190-192 °C; IR (KBr) 3125 cm^{-1} (OH), 2250 (NH^+); NMR ($CDCl_3$), free base, δ 0.9 (t, 6 H, 3'-CH_3), 1.5 (m, 4 H, 2'-CH_2), 2.5 (t, 4 H, 1'-CH_2), 2.8-3.5 (m, 3 H), 3.5-4.4 (m, 2 H), 6.3 (br, 1 H, OH), 6.4-6.8 (m, 3 H, ArH); MS (CI + NH_3), m/e 260 (M + 1). Anal. ($C_{15}H_{24}NO_2Cl$) C, H, N, Cl.

Estimation of pK_a Values. The negative logarithms of the compounds were determined by potentiometric titration as described by Albert and Serjeant.[22] For each compound three to four apparent pK_a values were determined.

Determination of 1-Octanol-Water Partition Coefficients. To obtain a measure of lipophilicity at physiological pH the 1-octanol-water distribution coefficients were determined at pH 7.4. The substances were dissolved in Na^+/K^+-phosphate buffer saturated with 1-octanol. After the mixture was shaken in a closed tube with 1-octanol saturated with phosphate buffer, the two phases were separated by centrifugation. The concentrations were determined by HPLC with electrochemical detection.[15] A 15-cm Nucleosil 5-C18 column was used for the separation.

Pharmacology. Determination of Metabolites of Dopamine. Female albino rats of a Wistar-derived strain (C.D.L., Groningen, The Netherlands) were used. The body weights of the rats varied from 180 to 220 g. The compounds were administered by intraperitoneal (ip) injection in a volume of 2.0 mL kg^{-1} of saline. After 1 h, during which time the behavioral effects were scored according the method of Costall et al.,[21] the rats were killed by cervical dislocation. The corpora striata were rapidly dissected, frozen on dry ice, and stored at -80 °C. Following weighing of the frozen samples, homogenization in 0.1 M perchloric acid, and centrifugation (3000-g, 7 °C, 15 min), the amounts of the metabolites HVA and DOPAC in the supernatants were determined according to the method of Westerink and Mulder[15] by use of purification on Sephadex G 10, separation on a reversed-phase (RP 18) HPLC column, and electrochemical detection.

Displacement of the Specific Binding of [^{3}H]-DP-5,6-ADTN in Rat Striatum. This assay which was performed with homogenized and washed membrane preparations from rat striatum tissue was carried out as described previously.[19] In each experiment the amount of [^{3}H]-DP-5,6-ADTN bound was determined in the absence (total) and presence (nonspecific) of 10^{-6} M (+)-butaclamol, the difference yielding specific [^{3}H]-DP-5,6-ADTN binding. The ability to compete with [^{3}H]-DP-5,6-ADTN was tested over a concentration range of 10^{-11}-10^{-4} M.

Displacement of the Specific Binding of [^{3}H]-N-0437 in Calf Striatal Membranes. The binding experiments were carried out according the procedure of Van der Weide et al.[20] Specific binding was defined as the difference in the amount of radioactivity in the absence or presence of 1 μM unlabeled N-0437. The ability to compete with [^{3}H]-N-0437 was tested over a concentration range of 10^{-11}-10^{-4} M.

Registry No. **3b**, 116005-03-9; **3b** (base), 116005-04-0; **5a**, 116004-97-8; **5a** (base), 116005-01-7; **5b**, 112960-16-4; **5b** (base), 112960-12-0; **6a**, 20351-79-5; **6b**, 5802-17-5; **8a**, 116004-85-4; **8b**, 116004-86-5; **10a**, 116004-87-6; **10a** (amine·HCl), 22406-62-8; **10b**, 116004-88-7; **10b** (amine·HCl), 22406-60-6; **11a**, 116004-89-8; *cis*-**11a**, 116004-90-1; **11b**, 116004-91-2; *cis*-**11b**, 116004-92-3; **12a**, 116025-07-1; **12b**, 116004-93-4; **13a**, 116004-94-5; **13a** (base), 116004-98-9; **13b**, 116004-95-6; **13b** (base), 116004-99-0; **14a**, 116004-96-7; **14a** (base), 116005-00-6; **14b**, 112960-15-3; **14b** (base), 112960-14-2; **15**, 116005-02-8; **15** (base), 110927-04-3; $ClCH_2COCl$, 79-04-9; n-C_3H_7I, 107-08-4; $C_2H_5CO_2H$, 79-09-4.

Retinobenzoic Acids. 1. Structure-Activity Relationships of Aromatic Amides with Retinoidal Activity

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Received March 14, 1988

Two types of aromatic amides, terephthalic monoanilides and (arylcarboxamido)benzoic acids, have been shown to possess potent retinoidal activities and can be classified as retinoids. The structure-activity relationships of these amides are discussed on the basis of differentiation-inducing activity on human promyelocytic leukemia cells HL-60. In generic formula 4 (X = NHCO or CONH), the necessary factors to elicit the retinoidal activities are a medium-sized alkyl group (isopropyl, *tert*-butyl, etc.) at the meta position and a carboxyl group at the para position of the other benzene ring. The bonding of the amide structure can be reversed, this moiety apparently having the role of locating the two benzene rings at suitable positions with respect to each other. Substitution at the ring position ortho to the amide group or N-methylation of the amide group caused loss of activity, presumably owing to the resultant change of conformation. It is clear that the mutual orientation of the benzylic methyl group(s) and the carboxyl group and their distance apart are essential factors determining the retinoidal activity. Among the synthesized compounds, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (Am80) and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid (Am580) were several times more active than retinoic acid in the assay. They are structurally related to retinoic acid, as is clear from the biological activity of the hybrid compounds (M2 and R2).

Retinoids are defined as "a class of compounds consisting of four isoprenoid units joined in head to tail manner.[1] All retinoids may be formally derived from a monocyclic parent compound (that is, retinol) ...". Biologically retinoids are substances that can elicit specific biological responses by binding to or activating a specific receptor or set of receptors.[2,3] Synthetic ligands, that is, synthetic retinoids, which have a better molecular fit to these putative receptors than retinoic acid does, may elicit stronger or more specific vitamin A activities than retinol or retinoic acid (**1**, Chart I).[4] The most important activities of retinoids are, certainly, the effects on the differentiation and proliferation of many types of cells.[5] The synthesis of potent new compounds with retinoidal activities should facilitate the application of retinoids to

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