was dried under high vacuum to give 12.3 g (58%) of a mixture of **10** and **11**. ^{1}H NMR ($CDCl_3$): δ 1.37 and 2.58 (2 d, CH_3CH), 2.7–4.3 (m, CH_2S, CHS, CH_2Cl, CHCl, CH_2N), and 7.5–8.2 (aromatic). Anal. ($C_{13}H_{14}ClNO_2S$) C, H, N.

6-Methoxy-4-methyl-8-[(1′-methyl-5′-phthalimido-3′-thiapentyl)amino]-5-[*m*-(trifluoromethyl)phenoxy]quinoline (13) and 6-Methoxy-4-methyl-8-[(2′-methyl-5′-phthalimido-3′-thiapentyl)amino]-5-[*m*-(trifluoromethyl)phenoxy]-quinoline (14). A misture of 7.0 g (0.02 mol) of 8-amino-6-methoxy-4-methyl-5-[*m*-(trifluoromethyl)phenoxy]quinoline (**12**)[1] and 2.85 g (0.01 mol) of the mixture of chloro compounds **10** and **11** was heated (oil bath) at 90–100 °C. Over the next 8 h, 9.15 g (0.032 mol) of the **10** and **11** mixture and 4.24 g (0.042 mol) of Et_3N were added gradually to the heated and stirred reaction mixture. After the addition was complete, the reaction mixture was heated at 90–100 °C an additional 17 h (25 h total). The cooled reaction mixture was dissolved in CH_2Cl_2 and washed with water. Concentration of the dried (Na_2SO_4) CH_2Cl_2 solution gave 19 g of a dark gum. This gum was chromatographed on 600 g of silica gel (Merck 60) using CH_2Cl_2–2% acetone as the eluent. The product fraction was fractionally crystallized from CH_3OH to give 2.84 g (24%) of **13** as light yellow crystals, mp 148–150 °C, and 1.13 g (9.5%) of **14** as bright yellow crystals, mp 106–109 °C.

The analytical sample of **13** prepared by recrystallization from CH_3OH had a melting point of 149–151 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (d, CH_3CH), 2.62 (s, CH_3Ar), 2.76–2.86 (m, CH_2SCH_2 and CHNH), 3.86 (s, CH_3O), 3.90 overlapped by 3.86 resonance (t, CH_2NPht), 6.59 (s, C-7), 6.80–7.46 (m, C-3 and $CF_3C_6H_4O$), 7.6–7.9 (m, NPht), 8.40 (d, C-2).

The analytical sample of **14** prepared by recrystallization from CH_3OH had a melting point of 108–110 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (d, CH_3CH) 2.62 (s, CH_3Ar), 2.7–3.1 (m, CH_2S, CHS), 3.3–3.7 (br peak, CH_2N), 3.86 (s, CH_3O), 3.92 overlapped by 3.86 resonance (t, CH_2NPht), 6.56 (s, C-7), 6.80–7.46 (m, C-3 and $CF_3C_6H_4O$), 7.6–7.9 (m, NPht), 8.40 (d, C-2). Anal. ($C_{31}H_{28}F_3N_3O_4S$) C, H, N for **13** and **14**.

The silica gel column was eluted with CH_2Cl_2 –5% acetone to give 3.5 g (50%) of recovered **12**.

The reaction was repeated on a 0.018-mol scale to give essentially the same results.

8-[(5′-Amino-1′-methyl-3′-thiapentyl)amino]-6-methoxy-4-methyl-5-[(*m*-(trifluoromethyl)phenoxy]quinoline (4) Fumarate. A solution of 3.5 g (0.0059 mol) of **13** in 150 mL of EtOH containing 1 g of hydrazine was refluxed for 2 h. The cooled reaction mixture was filtered and the solid washed with EtOH. The filtrate was concentrated and the resulting residue dried under vacuum. The residue was treated with CH_2Cl_2 and filtered. The filtrate was concentrated and the resulting oil dried under high vacuum overnight to give 2.86 g of **4** as a viscous orange-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, CH_3CH), 2.57 (s, CH_3Ar), 2.5–3.1 (m overlapping 2.57 resonance, CH_2S, CH_2N, and CHN), 3.78 (s, CH_3O), 6.4 (s, C-7), 6.7–7.3 (m, C-3 and $CF_3C_6H_4O$), 8.3 (d, C-2).

The oil was dissolved in 30 mL of isopropyl alcohol and warmed on a steam bath and 0.71 g of fumaric acid added. On cooling, the product separated as yellow crystals. Filtration and drying gave 3.2 g (94%) of product, mp 143–145 °C dec. Anal. ($C_{27}H_{30}F_3N_3O_6S$) C, H, N.

8-[(5′-Amino-2′-methyl-3′-thiapentyl)amino]-6-methoxy-4-methyl-5-[*m*-(trifluoromethyl)phenoxy]quinoline (5) Fumarate. Compound **14** was converted to **5** in the same manner as reported for **13**. From 2.5 g (0.0042 mol) of **14** was obtained, 2.0 g of **5**. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, CH_3CH), 2.25 (s, $ArCH_3$), 2.7–3.6 (CH_2,s, CH_2,n, CHS), 3.78 (CH_3O), 6.38 (s, C-7), 6.5–7.3 (m, C-3 and $CF_3C_6H_4O$), 8.32 (d, C-2).

The oil was dissolved in 20 mL of isopropyl alcohol and warmed on a steam bath and 0.51 g of fumaric acid added. On cooling, the product separated as cream crystals. Filtration and drying gave 2.4 g (99%) of product, mp 160–161 °C dec. Anal. ($C_{27}H_{30}F_3N_3O_6S\cdot H_2O$) C, H, N.

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Registry No. **4**, 98586-86-8; **4**·fumarate, 98586-94-8; **5**, 98586-87-9; **5**·fumarate, 98586-95-9; **7**, 574-98-1; **8**, 98586-88-0; **9**, 98586-89-1; **10**, 98586-90-4; **11**, 98586-91-5; **12**, 82329-72-4; **13**, 98586-92-6; **14**, 98586-93-7; mercaptoacetone, 24653-75-6; (*p*-bromophenyl)sulfonyl chloride, 98-58-8.

3,4-*O*-Diacetylisoproterenol. Preparation, Structure Proof, and β-Receptor Effect

Palle Jakobsen,*† Svend Treppendahl,† Peter H. Andersen,†,§ Rene Klysner,‡ Arne Geisler,‡ and Lene Teuber⊥

Department of Chemistry, Panum Institute, University of Copenhagen, DK-2200 Copenhagen N, Denmark, Department of Pharmacology, University of Copenhagen, DK-2100 Copenhagen Ø, Denmark, and Chemical Laboratory II, H. C. Ørsted Institute, University of Copenhagen, DK-2100 Copenhagen Ø, Denmark. *Received December 17, 1984*

Direct acetylation of isoproterenol by selective O-acetylation using CH_3COCl/CF_3COOH was shown to lead to the formation of 2-(3,4-diacetoxyphenyl)-2-chloro-*N*-isopropyl-1-ethanamine and not to 3,4-*O*-diacetylisoproterenol. The latter was prepared by reduction of 3,4-diacetoxy(2-isopropylamino)acetophenone and its structure confirmed by IR, ^{1}H, ^{13}C NMR, mass spectral, and elemental analysis. The two compounds were tested for activity on β-receptors. Efficacy and affinity on β_1-receptors were found identical with the effect of isoproterenol. So was efficacy on β_2-receptors, while affinity was lower for the chloro compound than for isoproterenol and diacetylisoproterenol which exhibited identical affinity.

In our recent investigation on cerebral subsensitivity in the β-adrenoceptor system following antidepressant treatment,[1] we needed a lipophilic β-agonist in order to investigate whether long-term treatment with such a compound would induce β-adrenoceptor subsensitivity in a way like the antidepressants. We decided to use 3,4-*O*-diacetylisoproterenol (**3**) since this compound has been described to cross the blood–brain barrier.[2]

Two methods for the synthesis of **3** are described in the literature: Dooley[2] reported the use of acetyl chloride in trifluoroacetic acid for selective O-acetylation of isopro-

† Panum Institute, University of Copenhagen.
‡ Department of Pharmacology, University of Copenhagen.
§ Present address: Novo Research Institute, Department of Experimental Pharmacology, DK-2880 Bagsvaerd, Denmark.
⊥ H. C. Ørsted Institute.

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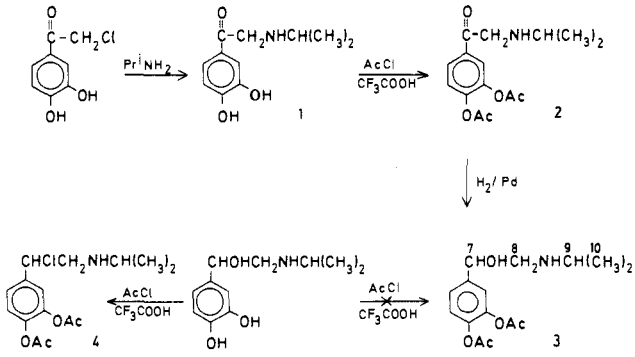
0022-2623/85/1828-1962$01.50/0

Scheme I



terenol, leading to a product claimed to be 3,4-*O*-diacetylisoproterenol (mp 166–169 °C). Another method by Bretschneider[4,5] gave a product, mp 198 °C, also said to be 3,4-*O*-diacetylisoproterenol, formed by reduction of the corresponding oxo compound. The compounds formed are obviously not identical, and in order to find the correct structure for the two compounds we used both methods, the latter with small modification, and characterized the products by IR, ^1H, ^{13}C NMR, mass spectral, and elemental analysis.

Preparation of **3** was carried out from ω-chloro-3,4-dihydroxyacetophenone and isopropylamine as depicted in Scheme I. The acetylation was performed by the selective O-acetylation described by Borgman,[3] and the final reduction to **3** was carried out by hydrogenation at atmospheric pressure for 8 h at 50 °C.

Direct acetylation of isoproterenol as described by Dooley afforded a crystalline trifluoroacetate of 2-(3,4-diacetoxyphenyl)-2-chloro-*N*-isopropyl-1-ethanamine (**4**), which on treatment with anion-exchange resin was converted to the hydrochloride of **4**. This in accordance with earlier reports[4,5] on the acetylation of epinephrine derivatives, which indicates that acetylation by means of acetyl chloride leads to substitution of the aliphatic hydroxy group with chlorine, in addition to acetylation of the phenolic groups.

The elemental analysis found for compounds **3** and **4** corresponded to the proposed compositions. Melting points were found to be ~198–200 and 165–166 °C, respectively, in accordance with the values found by Bretschneider[5] and Dooley.[2]

Spectroscopic Evidence. The main difference in the IR spectra of compounds **3** and **4** was the absence of OH stretching vibration in the spectrum of **4** while that of **3** had the OH band at 3340 cm^{-1}. This clearly indicates that compound **4** does not contain a free OH group. Dooley quoted the following ^1H NMR shift values (δ) for his compound: Ar, 7.6–7.3; CHO, 5.63; CH_2NCH, 3.8–3.2; CH_3CO, 2.27; $(CH_3)_2C$, 1.25.[2] We found the same signal pattern for compound **4** with only minor shift differences (see the Experimental Section). Shaking with D_2O failed however to change the signal pattern of the signal around 5.6 ppm ascribed by Dooley to the C*H*OH proton signal, for which the coupled pattern should change when the OH proton is exchanged for OD. For **3** the OH signal was found as a doublet at 6.32 ppm (disappeared on shaking with D_2O). The C*H*OH signal was found at 5.2–5.0 ppm as a multiplet (changed to a double doublet on treatment with D_2O). This is accordance with the chemical shift value for the C*H*OH proton in authentic isoproterenol found to 4.95 ppm in Me_2SO-d_6 solution. The other signals

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Table I. Affinity and Efficacy of Isoproterenol and Derivatives in Stimulating cAMP Synthesis by β_1 or β_2 Receptors[a]

compd	K_m, μM		efficacy	
	cerebral cortex	human platelets	cerebral cortex	human platelets
isoproterenol	32 ± 18	0.05 ± 0.012	1	1
diacetylisoproterenol (**3**)	25 ± 12	0.088 ± 0.022	1	1
chlorodiacetyl-isoproterenol (**4**)	28 ± 9	0.620 ± 0.074	1	1

[a] Results shown as mean SD (N = 2–3).

(see the Experimental Section) were found in the same area for compounds **3** and **4**.

The ^{13}C NMR spectra of **3** and **4** showed the expected difference in the chemical shift values for the aromatic carbon atoms and C-7 (see Scheme I). In the chloro compound C-7 was found at 57.2 ppm, while the corresponding carbon atom in **3** was found at 67.7 ppm in accordance with the value for authentic isoproterenol, 68.4 ppm (in Me_2SO-d_6) and 69.8 ppm (in D_2O),[6] and for other (phenylamino)ethanol derivatives.[6] By use of literature values for shielding effects for substituents in aromatic systems,[7] the assignment that appear in the Experimental Section was carried out. Off-resonance decoupling experiments were carried out to facilitate the assignment for both compounds.

The mass spectrum of **3** showed the molecular ion at m/e 295 corresponding to the free base while the molecular ion for **4** was m/e 313 with an isotope peak at m/e 315 showing the content of Cl in the free base. The degradation pattern was found in accordance with the proposed structure for both compounds.

Pharmacological Data. Isoproterenol, diacetylisoproterenol **3**, and chlorodiacetylisoproterenol **4** were tested on tissue preparations containing mainly β_1 or β_2 receptors. As a β_1-containing tissue, we used rat cortical slices;[10] β_1-stimulated cAMP accumulation in this preparation is fully blocked by the β_1-selective antagonist metoprolol but not stimulated by β_2-selective agonists, i.e. tertbutaline and salbutamol (not shown). As β_2-containing tissue we used human platelets that previously have been shown to contain only this receptor subtype.[11] All three compounds exhibited identical affinity and efficacy in the rat cerebral slice preparation (Table I), indicating that neither the acetylation nor the chloro substitution has influence on the activity on the β_1 receptor. In the platelet preparation isoproterenol and diacetylisoproterenol **3** exhibited identical affinity and efficacy while chlorodiacetylisoproterenol **4** had substantially lower affinity but an efficacy identical with isoproterenol. Thus, a chloro substitution for the OH at C-7 decreases the affinity for the β_2 receptor.

Conclusion. The chemical and spectroscopical evidence clearly proves that the compound prepared by direct acetylation of isoproterenol has structure **4** and consequently diacetylisoproterenol cannot be prepared by this

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method. This means that the Borgman acetylation method[3] must be used with care when aliphatic hydroxy groups are present in the molecule, as was described for the acetylation method used by Bretschneider.[4,5] The ^{13}C chemical shift value of C-7 as found in the area 66.8–70.3 ppm for different (phenylamino)ethanol derivatives including **3**, compared to the value 57.2 ppm found in **4** for C-7, seems to be valuable for structure proof. The ^{13}C signals for the methyl carbons of the isopropyl groups were found magnetically nonequivalent for both **3** and **4**. This is in accordance with results for other isopropylamino groups containing compounds with a chiral center.[6,8] It has been ascribed to the asymmetric effect of the chiral center that is transmitted across the nitrogen atom causing the nonequivalence.[6]

On basis of our experiments it seems reasonable to point out that when using diacetylisoproterenol of unknown origin it should be checked by spectroscopic methods and/or by estimation of melting point. The two compounds **3** and **4** have different affinity on the β_2 receptor but exhibit identical characteristics, and their effect on the β_1-receptor is identical.

Experimental Section

Microanalyses were carried out in the Microanalysis Department, Chemical Laboratory II, The H. C. Ørsted Institute. IR spectra were recorded on the Perkin-Elmer Model 298 infrared spectrophotometer. Mass spectra were obtained on an AEI-902 instrument operating at 70 eV. ^1H and ^{13}C NMR spectra were recorded on ca. 100 mg/0.5 mL solutions in Me_2SO-d_6 on a JEOL FX 90Q apparatus. Melting poins are uncorrected.

3′,4′-Dihydroxy-2-(isopropylamino)acetophenone Hydrochloride[9] **(1)**: recrystallized from absolute ethanol; mp 250–253 °C. Anal. ($C_{11}H_{16}ClNO_3$) C, H, N. Yield 46%; ^1H NMR (Me_2SO-d_6) δ 1.30 (6 H, d), 3.1–3.6 (1 H, m), 4.56 (2 H, s), 6.8–7.6 (3 H, m), 9.0 (2 H, br), 9.6 (1 H, br), 10.3 (1 H, br); ^{13}C NMR (Me_2SO-d_6) δ 190.3, 152.2, 145.6, 125.5, 121.9, 115.4, 115.1, 49.7, 48.9, 18.5.

3′,4′-Diacetoxy-2-(isopropylamino)acetophenone Hydrochloride (2): 1 (0.024 mol) was dissolved in CF_3COOH (50 mL) at 0 °C. Acetyl chloride (0.135 mol) was added and the mixture heated to 50 °C for $^1/_2$ h. The mixture was subsequently evaporated to dryness, dissolved in 2-propanol (20 mL), and evaporated again. The residue was dissolved in absolute ethanol (150 mL) and stirred with 40-g of anion-exchange resin (BIO-RAD AG 2-X8, 20–50 mesh, chloride form) for 1 h. The filtrate was evaporated to dryness and recrystallized from absolute ethanol: yield 55%; mp 208–210 °C. Anal. ($C_{15}H_{20}ClNO_5$) C, H, N. ^1H NMR (Me_2SO-d_6) δ 1.31 (6 H, d), 2.33 (6 H, s), 3.1–3.6 (1 H, m), 4.74 (2 H, s), 7.4–8.1 (3 H, m), 9.24 (2 H, s, br); ^{13}C NMR (Me_2SO-d_6) δ 190.9, 168.0, 167.7, 146.8, 142.3, 132.2, 127.1, 124.3, 123.7, 49.7, 49.4, 20.3, 20.2, 18.4.

3,4-*O*-Diacetylisoproterenol Hydrochloride (3): prepared from **2** according to the literature;[5] recrystallized from absolute ethanol; yield 55%; mp 198–200 °C. Anal. ($C_{15}H_{22}ClNO_5$) C, H, N, Cl. IR (KBr, cm^{-1}) 3340 (m, br), 2920 (w), 2770 (w, br) 1768 (s), 1559 (w), 1500 (m), 1425 (w), 1370 (m), 1255 (m), 1205 (s), 1170 (s), 1150 (m), 1110 (m), 1055 (w), 1011 (m), 900 (m), 841 (m), 809 (w); ^1H NMR (Me_2SO-d_6) δ 8.6–7.4 (NH_2) (2 H, br), 7.33 (aromatic) (3 H, m), 6.32 (OH) (1 H, d) disappear on shaking with D_2O, 5.2–5.0 (C*H*OH) (1 H, m), 3.5–2.7 (CH + CH_2) (3 H, m), 2.28 (CH_3CO) (6 H, s), 1.27 (3 H, d) and 1.25 (3 H, d) ((CH_3)$_2$CH); ^{13}C NMR (Me_2SO-d_6) δ 140.6 (C-1), 123.4 (C-2), 141.2 (C-3), 141.9 (C-4), 121.0 (C-5), 124.1 (C-6), 67.7 (C-7), 50.7 (C-8), 49.7 (C-9), 18.6 (C-10), 18.0, 168.1 (CH_3CO), 20.3 (CH_3CO); mass spectrum *m/e* (% base peak) 295 (16, M^+), 220 (7), 181 (7), 139 (24), 138 (9), 93 (15), 73 (60), 72 (100), 70 (10), 65 (14), 58 (19), 57 (19), 56 (23), 46 (11), 45 (20), 44 (17), 43 (100), 42 (11), 41 (31).

2-(3,4-Diacetoxyphenyl)-2-chloro-*N*-isopropyl-1-ethanamine Hydrochloride (4): prepared according to the literature;[2] mp 165–166 °C; yield 40%. Anal. ($C_{15}H_{21}Cl_2NO_4$) C, H, N, Cl. IR (KBr, cm^{-1}) 2980 (m), 2940 (m), 2790–2670 (br), 1772 (s), 1505 (m), 1403 (m), 1370 (m), 1260 (m), 1205 (s), 1180 (s, sh), 1110 (m), 1011 (w), 900 (w); ^1H NMR (Me_2SO-d_6) δ 9.99 (1 H, br) and 9.32 (1 H, br) (NH_2), 7.9–7.5 (Ar) (3 H, m), 6.00 (d) and 5.94 (d), (1 H, J = 8.5 Hz) (C*H*ClCH_2). [This chemical shift value was found dependent on the water content, moving toward higher field with increasing water content. On shaking with D_2O the coupling pattern was unchanged, and the chemical shift value was 5.6 ppm.] 3.9–3.2 (CH_2NH_2CH) (3 H, m), 2.29 (CH_3CO) (6 H, s), 1.31 (3 H, s) and 1.27 (3 H, d J = 7 Hz) (CH_3)$_2$CH; ^{13}C NMR (Me_2SO-d_6) δ 142.5, 142.0, 136.2, 125.9, 124.1, 122.8, 57.2 (C-7), 50.0 (C-8), 50.5 (C-9), 18.6 and 17.9 (C-10), 167.9 (CH_3CO), 20.2 (CH_3CO); mass spectrum *m/e* (% of base peak) 315 (1), 313 (4, M^+), 237 (10), 238 (21), 218 (13), 192 (44), 188 (14), 151 (13), 150 (53), 136 (27), 123 (18), 77 (13), 73 (45), 72 (100), 56 (15), 44 (16), 43 (100), 41 (21).

Blood Platelet Preparation. Blood samples were collected from healthy drug-free volunteers, and the platelets were isolated and incubated as described previously.[12]

Cyclic AMP Determination. The cAMP content was determined by a protein binding method.[13]

Slice Preparation. Cerebral tissue for determination of cyclic AMP accumulation was chopped with a microtome to a thickness of 300 μm. After a 45° rotation of the table the tissue was chopped again. Subsequently the tissue was suspended in 20 mL of a Krebs–Ringer buffer with the following composition: NaCl, 122 mM; KCl, 3 mM; $CaCl_2$, 1.3 mM; $MgSO_4$, 1.2 mM; KH_2PO_4, 0.4 mM; D-glucose, 10 mM; $NaHCO_3$, 25 mM; Na_2EDTA, 10 mM. This buffer had previously been gassed with 95% O_2–5% CO_2 to pH 7.3–7.4. The tissue preparation was then preincubated for 60 min at 37 °C in an atmosphere of 95% O_2–5% CO_2 with changes of buffer every 20 min. After 1 h, the tissue suspension was diluted and 50-μL aliquots were transferred to beakers continuously gassed with 95% O_2–5% CO_2. Buffer or isoproterenol (or derivatives) and buffer were added, and the incubation was continued for 15 min. The incubation was stopped by boiling the tissue for 10 min. The samples were then spun in the cold, and the clear supernatant was stored at −20 °C until determination of cyclic AMP.

Registry No. 1·HCl, 16899-81-3; **2**·HCl, 98634-90-3; **3**, 35553-62-9; **3**·HCl, 55508-67-3; **4**, 98634-91-4; **4**·HCl, 98651-83-3; ω-chloro-3,4-dihydroxyacetophenone, 99-40-1; 2-(3,4-dihydroxyphenyl)-2-hydroxy-*N*-isopropyl-1-ethanamine, 7683-59-2.

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