Sulfur-Interrupted 8-Amino Side Chain Analogues of 4-Methyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine as Potential Antimalarial Agents

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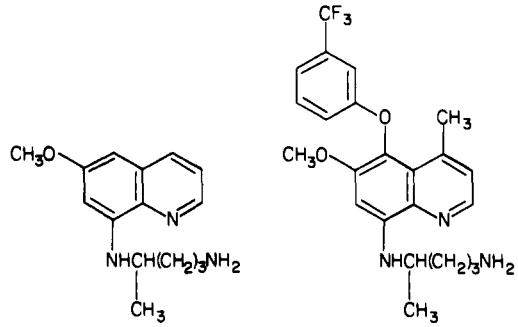
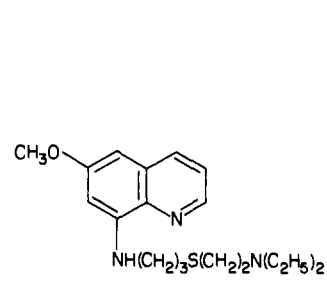
Two isomeric sulfur-interrupted 8-amino side chain analogues of 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (2) were prepared and tested for antimalarial activity. The compounds were evaluated for blood schizonticidal activity against *Plasmodium berghei* in mice and radical curative activity against *Plasmodium cynomolgi* in rhesus monkeys. In addition, they were evaluated for causal prophylactic activity against *Plasmodium berghei yoelii* in mice. Both compounds were more active and less toxic than primaquine in the *P. berghei* screen. One of the compounds showed radical curative activity similar to primaquine but was less active than 2. One of the compounds was active at 160 mg/kg in the *P. berghei yoelii* screen; the other was not active.

Primaquine (1) is still the only drug available for the treatment of *Plasmodium vivax*. The major drawback of primaquine is its low therapeutic index. Recently, 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (2) was reported to have significantly better therapeutic index than 1[1] as judged by results from *Plasmodium berghei* screen in mice and *Plasmodium cynomolgi* test in monkeys.



1 2

The effect on antimalarial activity of variations of the position 8 side chain of 8-aminoquinolines has been summarized.[2,3] The results showed that the type of toxicity induced by the 8-aminoquinolines depends to a large degree upon the structure of the side chain. An examination of antimalarial test results listed by Wiselogle,[3] Coatney and co-workers,[4] and Thompson and Werbel[5] showed that certain 8-aminoquinolines such as 8-[[6′-(diethylamino)-4′-thiahexyl]amino]-6-methoxyquinoline (3), which contains a thioether linkage in the side chain, retained good activity against *Plasmodium lophurae* in the duck, *Plasmodium gallinaceum* in the chick, and *Plasmodium cathemerium* in the canary. However, apparently no new compounds possessing a thioether linkage in the 8-aminoalkyl side chain have been prepared and evaluated for antimalarial activity. In particular, no compounds containing a terminal primary amino group or a branched thioether-containing side chain have been prepared. In this report we describe the synthesis of 8-[(5′-amino-1-methyl-3′-thiapentyl)amino]-6-methoxy-4-methyl-5-[*m*-(trifluoromethyl)phenoxy]quinoline (4) and 8-[(5′-amino-2′-methyl-3′-thiapentyl)amino]-6-methoxy-4-methyl-5-[*m*-(trifluoromethyl)phenoxy]quinoline (5), both of which are sulfur-interrupted 8-amino side chain analogues of 2.



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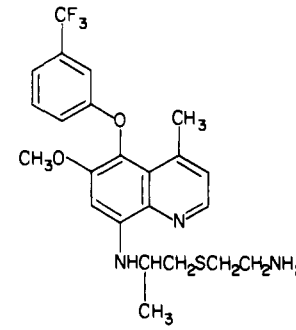

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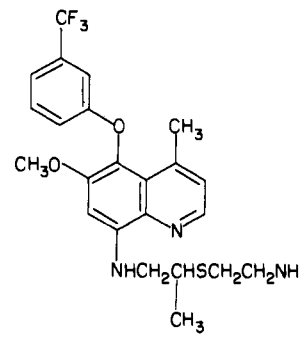

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Chemistry. The two sulfur-interrupted side chain analogues 4 and 5 of the highly active antimalarial 2 were prepared as shown in Chart I. Alkylation of mercaptoacetone[6] (6) with (2-bromoethyl)phthalimide (7) yielded the keto sulfide 8. Sodium borohydride reduction of 8 afforded the hydroxy sulfide (9). Treatment of 9 with (*p*-bromophenyl)sulfonyl chloride in pyridine resulted in the isolation of the mixture of chloro sulfides 10 and 11. Alkylation of the 8-amino-6-methoxy-5-[*m*-(trifluoromethyl)phenoxy]quinoline (12)[1] with this mixture of chloro sulfides gave the phthaloyl-protected sulfur-interrupted chain analogues 13 and 14 which were separated by fractional crystallization. The structures of 13 and 14 were established via ^{13}C NMR studies (see Table I). Treatment of 13 and 14 with hydrazine in ethanol gave the target compounds 4 and 5, respectively.

Biological Testing. The data in Tables II and III compare the activities of 4 and 5 to those of primaquine (1) and the 4,5-disubstituted primaquine analogue 2 in the

(1) Strube, R. E.; LaMontagne, M. P. U.S. 4431807, 1984. 4431807.
(2) Russell, P. B. "Medicinal Chemistry", 2nd ed.; Burger, A., Ed.; Interscience: New York, 1960; p 814.
(3) Wiselogle, F. Y. "Survey of Antimalarial Drugs, 1941–1945"; J. W. Edwards: Ann Arbor, MI, 1946; Vol. I, p 117.
(4) Coatney, G. R.; Cooper, W. C.; Eddy, N. B.; Greenberg, J. "Survey of Antimalarial Agents", Public Health Monograph No. 9; Washington, DC, 1953, p 52.
(5) Thompson, P. E.; Werbel, L. M. "Medicinal Chemistry"; de-Stevens, G., Ed.; Academic Press: New York, 1972; Vol. 12, p 105.
(6) Hromatka, V. O.; Engel, E. *Montasch. Chem.* 1948, *78*, 32.

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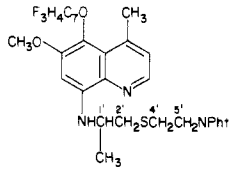
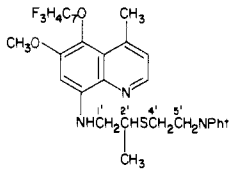
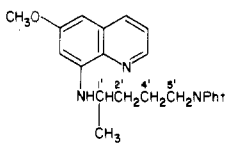
Table I. Comparison of ^{13}C NMR Data for 13 and 14 to *N*-Phthaloylprimaquine[a,b]

compd	carbon[c] 1	2	4	5	CH_3	CH_3O	CH_3Ar
 13	48.3 (d)	36.9 (t)	30.9 (t)	37.9 (t)	20.2 (q)	56.5 (q)	23.0 (q)
 14	48.9 (t)	39.0 (d)	28.2 (t)	37.4 (t)	19.5 (q)	56.5 (q)	23.0 (q)
	47.7 (d)	33.8 (t)	25.3 (t)	37.8 (t)	20.4 (q)	55.1 (q)	

[a] Spectra were obtained in $CDCl_3$. [b] Chemical shifts are in parts per million relative to Me_4Si. [c] Signal multiplicity obtained from single frequency off-resonance experiment: s = singlet, d = doublet, t = triplet, q = quartet. [d] This compound is numbered to correspond to 13 and 14.

Table II. Antimalarial Activity against *Plasmodium berghei* in Rodents[a]

compd	ΔMST, C or T:[b] dose, mg/kg 5	10	20	40	80	160	320	640
$1 \cdot 2H_3PO_4$					9.0	2 T	5 T	5 T
2[c]	1 C	3 C	5 C	5 C	5 C	5 C	5 C	1 C, 4 T
4			3.0	2.0	6.6	6.8	9.6 (1C)	12.3 (1 T, 2 C)
5				0.5	1.5	4.5	6.5 (1 C)	9.7

[a] Tests were carried out by the Rane Laboratory, University of Miami, Miami, FL, using blood-induced *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[7] Test data were supplied by Dr. E. A. Steck of Walter Reed Arym Institute of Research. [b] ΔMST, mean survial time over controls (6.2 ± 0.5 days). A compound is considered active if MST of the treated group is more than twice that of the control group: C, number of cures (mice surviving 60 days); T, number of toxic deaths occurring on days 2–5 after infection. [c] Taken from ref 1.

Table III. Antimalarial Activities against *Plasmodium cynomolgi* in Rhesus Monkeys[a,b]

compd	dose,[c] mg/kg	cures[d]	relapses[e]
1[f]	0.1	0/2	
	0.316	0/2	
	1.0	1/2	
2[f]	0.1	0/1	
	0.316	2/2	
	1.0	2/2	
4	0.1	0/2	8, 13
	0.316	0/2	28, 54
	1.0	1/2	18
5	0.1	0/2	7, 7
	1.0	0/2	7, 20

[a] Data were supplied by H. A. Musallam and B. T. Poon, Walter Reed Army Institute of Research. [b] Tests were carried out by SEATO Medical Research Laboratory, Bangkok.[8,9] [c] Dose administered via stomach tube once daily for 7 days with 5 mg of base/kg of chloroquine. [d] Monkeys that did not relapse are considered cured (see ref 8). [e] The number given is the days between the end of treatment and relapse. [f] Taken from ref 1.

blood schizonticidal[7] and radical curative[8,9] antimalarial screens, respectively. Compounds **4** and **5** were more active and less toxic than primaquine but were less active than **2** in the blood schizonticidal screen. In the radical curative test **4** showed activity similar to primaquine but was less active than **2**. Compound **5** was not active at 0.1 and 1.0 mg/kg.

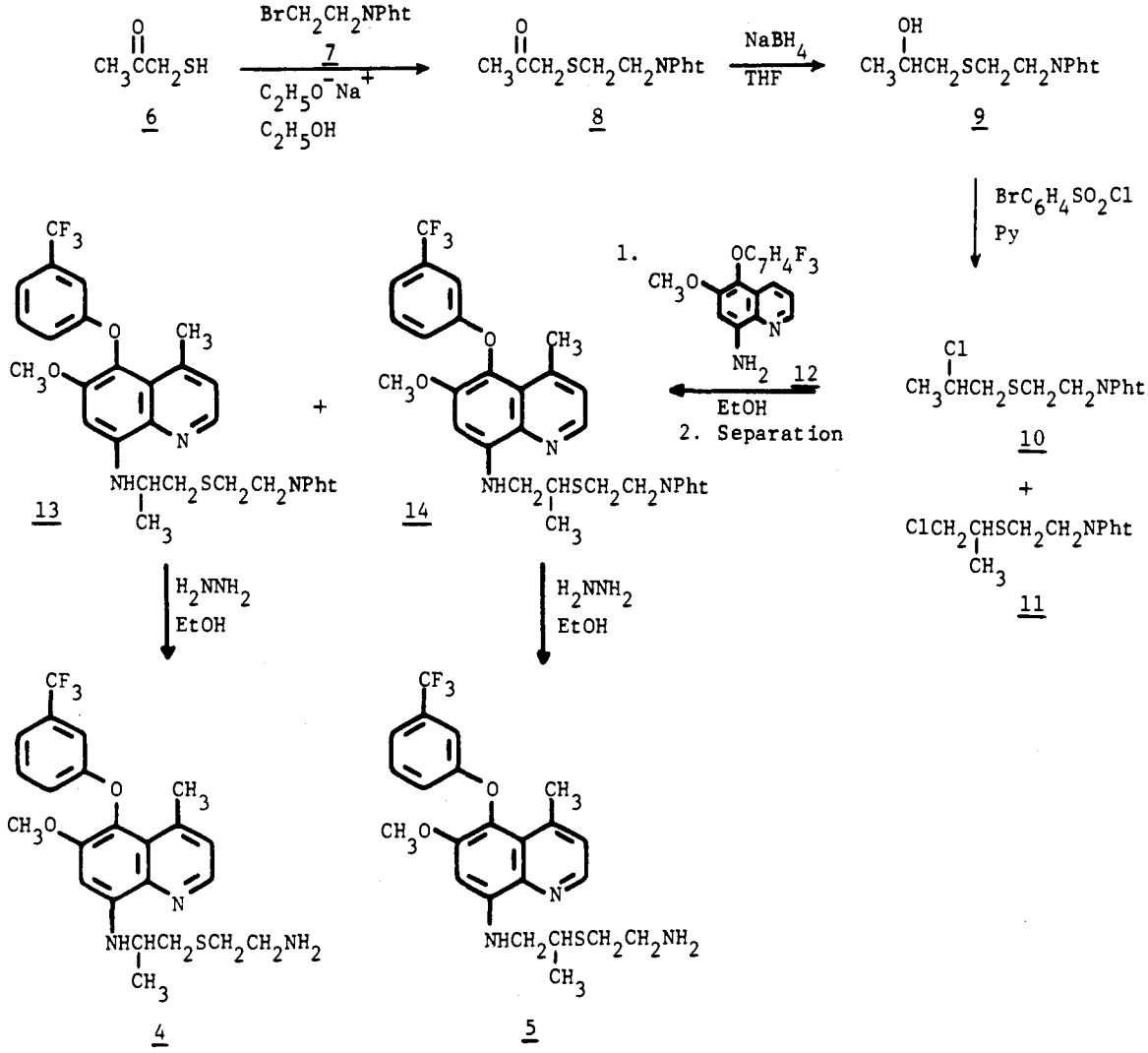
Table IV. Antimalarial Activity against *Plasmodium berghei yoelii* in Rodents[a]

compd	dose, mg/kg	cures sc	cures po	toxic
4	2.5	0/5	0/5	
	10	5/30	2/20	
	40	7/30	7/20	2 sc
	160	8/30	19/20	3 sc
5	10	0/15	0/5	
	40	1/15	0/5	1 sc
	160	5/15	0/5	1 sc

[a] These tests were carried out by the Rane Laboratory, University of Miami, Miami, FL, using sporozoite-induced *P. berghei yoelii* infected mice.[10,11] The test compound was dissolved or suspended in 0.5% (hydroxyethyl)cellulone–0.1% Tween 80 and administered either orally (po) or subcutaneously (sc) at several dose levels to groups of five mice on the day of challenge. Prophylactic activity is evidenced by survival of drug-treated mice to 30 days. Survival of 40% or more of the nice in the treated group may be considered as an indication of activity.

(7) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.
(8) Schmidt, L. N.; Rossan, R. N.; Fradkin, R.; Woods, J. *Bull. W.H.O.* **1966**, *34*, 783.
(9) The test procedure is described in World Health Organization (1972b), WHO/MAL/72.763 (cyclostyled report), World Health Organization, Geneva.

Chart I



Compounds **4** and **5** also were tested for causal prophylactic activity against sporozoite-induced *Plasmodium berghei yoelii* in rodents[10,11] (see Table IV). Compound **4** was active at 160 mg/kg when administered orally (19/20 curves).

The above test results indicate that the primaquine-type side chain ((4-amino-1-methylbutyl)amino) is superior to a sulfur-interrupted side chain even when it contains terminal amino group. In regard to this, LaMontagne and Blumbergs reported that the antimalarial activity of **2** was superior to that of five other 8-amino side chain analogues of **2**.[12]

Experimental Section

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, IL, or Integral Microanalytical Laboratories, Inc., Raleigh, NC.

5-Oxo-1-phthalimido-3-thiahexane (8). A solution of sodium ethoxide in EtOH was prepared by adding 2.3 g (0.1 mol) of sodium to 400 mL of EtOH. Mercaptoacetone[6] (**6**; 9.0 g, 0.10 mol) and (2-bromoethyl)phthalimide (**7**; 25.4 g, 0.1 mol) were added to the solution and the mixture was refluxed for 1 h. The reaction mixture was diluted with water and extracted with Et_2O. The extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was dried under high vacuum to give 24.2 g (92%) of **8** as white crystals. The analytical sample prepared by recrystallization from EtOH had a melting point of 75–76 °C. Anal. ($C_{13}H_{13}NO_3S$) C, H, N.

5-Hydroxy-1-phthalimido-3-thiahexane (9). To an ice-cooled solution of 24.1 g (0.92 mol) of **8** in 600 mL of THF was added 10 g of $NaBH_4$. After 2 h at 0 °C and 2 h at 25 °C, an additional 10 g of $NaBH_4$ was added, and the reaction mixture was heated in a water bath at 50 °C for 2 h to complete the reduction. The THF was removed on a rotary evaporator. The residue was diluted with cold (0 °C) water and extracted with Et_2O. The extracts were washed with H_2O and saturated NaCl solution. Concentration of the dried (Na_2SO_4) extracts followed by drying of the residue under high vacuum gave 19.8 g (81%) of **9** as a light yellow oil. ^1H NMR ($CDCl_3$): δ 1.22 (d, CH_3CHO), 2.5–3.0 (m, CH_2SCH_2), 3.5–4.2 (m, CHO and CH_2N), 7.3–7.9 (m, aromatic). Anal. ($C_{13}H_{15}NO_3S$) C, H.

5-Chloro-1-phthalimido-3-thiahexane (10) and 1-Chloro-2-methyl-5-phthalimido-3-thiapentane (11). To an ice-cooled solution of 19.8 g (0.075 mol) of **9** in 60 mL of pyridine was added 22 g (0.086 mol) of (*p*-bromophenyl)sulfonyl chloride. The reaction mixture was allowed to warm to 25 °C and remain at this temperature for 3 h. The reaction mixture was diluted with cold (0 °C) water and extracted with Et_2O. The extracts were washed with cold water, cold 5% HCl solution, cold water, and cold saturated NaCl solution. The dried (Na_2SO_4) extracts were concentrated on a rotary evaporator, and the residue obtained

(10) Mort, H.; Montouri, W. *Am. J. Trop. Med. Hyg.* **1975**, *24*, 179.
(11) Kinnamon, K. E.; Rane, D. S. *Am. J. Trop. Med. Hyg.* **1979**, *28*, 937.
(12) LaMontagne, M. P.; Blumbergs, P. *J. Heterocycl. Chem.* **1984**, *21*, 33.

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

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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-

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(1) Geisler, A.; Klysner, R. *Acta Pharmacol. Toxicol.*, in press.
(2) Dooley, D. J.; Hungar, A. A.; Nelson, W. L.; Bowden, D. M. *Eur. J. Pharm.* **1981**, *70*, 213.
(3) Borgman, R. J.; Smith, R. V.; Keiser, J. E. *Synthesis* **1975**, 249 and references cited therein.

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