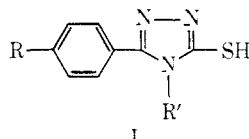


4-Alkyl-5-aryl-4*H*-1,2,4-triazole-3-thiols as Hypoglycemic AgentsM. Y. MHASALKAR, M. H. SHAH, S. T. NIKAM, K. G. ANANTANARAYANAN, AND C. V. DELIWALA<sup>1</sup>*Haffkine Institute, Bombay 12, India*

Received November 22, 1969

Twenty-one 4-alkyl-5-aryl-4*H*-1,2,4-triazole-3-thiols have been synthesized and screened for hypoglycemic activity in rats. Five compounds showed significant activity of which 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol and 5-*p*-sulfamoylphenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol were the most active, having a long duration of action and producing blood sugar lowering in normal as well as alloxan-treated rats. They had a very low order of toxicity and showed no antibacterial action.

We described earlier<sup>2,3</sup> the synthesis and diuretic activity of various substituted 3-mercapto-4*H*-1,2,4-triazoles. During the screening of these compounds for possible hypoglycemic effect, some showed significant activity. The most active of these was 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (I, R = Cl; R' = C<sub>2</sub>H<sub>5</sub>). The shifting of the Cl atom from the *para* to the *meta* position or its elimination lowered the hypoglycemic activity, while shifting the Cl atom to the *ortho* position abolished the activity. The work



R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, Cl, F, NO<sub>2</sub>, NH<sub>2</sub>, and SO<sub>2</sub>NH<sub>2</sub>  
 R' = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, *n*(or *i*)-C<sub>4</sub>H<sub>9</sub>, *n*(or *i*)-C<sub>6</sub>H<sub>13</sub>, C<sub>6</sub>H<sub>11</sub>, and CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>

has now been extended further and a number of related 4,5-disubstituted-4*H*-1,2,4-triazole-3-thiols have been synthesized to exploit the lead.

**Chemistry.**—1-Aroyl-4-alkylthiosemicarbazides were prepared from the requisite benzhydrazides and isothiocyanates and then cyclized with aq NaOH to get the corresponding triazoles. 5-*p*-Aminophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol was obtained by the reduction of the corresponding *p*-nitrophenyl analog. *p*-Ethylbenzhydrazide was obtained from ethyl *p*-ethylbenzoate.

**Hypoglycemic Activity.**—Of the 21 compounds synthesized and screened in normal rats at a dose level of 25 mg/kg, 5 compounds (**21**, **22**, **29**, **30**, **31**) showed blood sugar reduction of 30% or more and the blood

TABLE I  
COMPARATIVE HYPOLYCEMIC ACTIVITY OF **21**  
AND TOLBUTAMIDE IN RATS<sup>a</sup>

Hr	Percentage reduction in blood sugar		Prob- ability
	Compound <b>21</b> Mean (±SE)	Tolbutamide Mean (±SE)	
1.5	8.06 (±0.80)	12.60 (±0.67)	<0.001
3	16.08 (±1.23)	18.55 (±0.68)	NS
5	26.26 (±1.54)	26.76 (±0.79)	NS
7	34.75 (±2.00)	20.99 (±1.23)	<0.001
9	46.73 (±2.66)	15.37 (±0.94)	<0.001
24	39.01 (±1.75)	3.61 (±0.58)	<0.001

<sup>a</sup> Crossover tests at 25 mg/kg (oral) using 14 animals (7 per group).

(1) To whom the inquiries should be addressed.

(2) M. H. Shah, V. M. Patki, and M. Y. Mhasalkar, *J. Sci. Ind. Res., Sect. C*, **21**, 76 (1962).

(3) M. H. Shah, M. Y. Mhasalkar, V. M. Patki, and C. V. Deliwala, *J. Pharm. Sci.*, **58**, 1398 (1969).

TABLE II  
COMPARATIVE HYPOLYCEMIC ACTIVITY OF **30**  
AND TOLBUTAMIDE IN RATS<sup>a</sup>

Hr	Percentage reduction in blood sugar		Prob- ability
	Compound <b>30</b> Mean (±SE)	Tolbutamide Mean (±SE)	
1.5	10.50 (±1.39)	9.29 (±0.62)	NS
3	16.90 (±1.99)	16.90 (±0.78)	NS
5	28.05 (±3.00)	25.08 (±0.90)	NS
7	36.15 (±2.98)	20.54 (±1.21)	<0.001
9	45.27 (±2.27)	15.16 (±1.14)	<0.001
24	36.21 (±1.88)	3.03 (±0.66)	<0.001

<sup>a</sup> Crossover tests at 25 mg/kg (oral) using 14 animals (7 per group).

TABLE III  
BLOOD SUGAR REDUCTION IN ALLOXAN-DIABETIC RATS BY  
COMPOUNDS **21** AND **30** AT 25 MG/KG (ORAL)

Hr	Percentage blood sugar reduction <sup>a</sup> (±SE)	
	<b>21</b>	<b>30</b>
1.5	1.6 ± 0.70	6.3 ± 1.20
3	8.1 ± 2.02	17.8 ± 1.17
5	19.0 ± 0.89	20.9 ± 1.39
7	29.9 ± 2.10	24.8 ± 1.06
9	34.0 ± 1.40	28.1 ± 0.39
24	38.3 ± 0.95	23.6 ± 0.73

<sup>a</sup> Figures indicate mean values of 6 rats. Average fasting levels for **21** and **30** were 338 and 259.6 mg %, respectively.

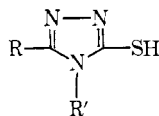
sugar value returned to normal only after 48 hr. A study of the effect of substitutions in the 4 position revealed that Et and methoxyethyl gave the most active compounds, while *n*-Bu and cyclohexyl were the next best. Further, whereas the 5-*p*-nitrophenyl derivative **38** possessed substantial activity, the corresponding 5-*p*-aminophenyl derivative **39** was practically inactive. Two of the most active compounds in this series, *viz.*, 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (**21**) and 5-*p*-sulfamoylphenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (**30**), were further tested at 10 mg/kg as well as at 50 mg/kg dose levels and produced significant blood sugar lowering. The crossover tests of these compounds with tolbutamide in rats at 25 mg/kg indicated that while the maximum reduction in blood sugar with tolbutamide was 25–27% at the end of the 5th hr, **21** and **30** produced a reduction of up to 45–47% at the 9th hr and even after 24 hr a good hypoglycemic effect was in evidence (Tables I and II). In alloxan-diabetic rats **21** and **30** also produced hypoglycemic responses of 34 and 28%, respectively, at the end of 9 hr and even after 24 hr significant reduction of blood sugar was present (Table III). When tested in rabbits, however, the activity of **21** and **30** was found to be of lower order (13.2 and 15.5%, respectively, at 25 mg/kg dose). These two compounds did not show any

TABLE IV  
1-ARYL-4-ALKYLTHIOSEMICARBAZIDES  
RCONHNHCSNHR'

No.	R	R'	Yield, %	Mp. °C	Formula <sup>a</sup>
1	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	73	196-197	C <sub>9</sub> H <sub>10</sub> ClN <sub>3</sub> OS
2	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	85	186-187	C <sub>11</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>2</sub> S <sup>b</sup>
3	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	75	178-179	C <sub>10</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub> OS <sup>c</sup>
4	4-FC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	94	190-191	C <sub>10</sub> H <sub>12</sub> FN <sub>3</sub> OS
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	91	194-195	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> OS
6	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	89	165-166	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> OS
7	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	85	158-159	C <sub>12</sub> H <sub>19</sub> N <sub>3</sub> OS
8	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>11</sub>	87	210-211	C <sub>13</sub> H <sub>21</sub> N <sub>3</sub> OS
9	4-C <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	78	174-175	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> OS
10	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	92	225-226	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>
11	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	90	186-187	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub>
12	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	90	211-213	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
13	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	84	208-209	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
14	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	89	209-210	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
15	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	93	200-201	C <sub>12</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
16	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>i</i> -C <sub>4</sub> H <sub>9</sub>	83	201-203	C <sub>12</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
17	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>11</sub>	88	214-216	C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>
18	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	93	200-201	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> S <sup>d</sup>

<sup>a</sup> All compounds were analyzed for N, S. <sup>b</sup> Calcd: N, 14.60. Found: 14.14. <sup>c</sup> Calcd: N, 14.38. Found: 14.83. <sup>d</sup> Calcd: N, 20.36. Found: 20.79.

TABLE V  
4-ALKYL-5-ARYL-4H-1,2,4-TRIAZOLE-3-THIOLS



No.	R	R'	Yield, %	Mp. °C	Formula	Analyses	Maximum blood sugar reduction at a dose of 25 mg/kg % (hr) <sup>a</sup>
19	4-ClC <sub>6</sub> H <sub>4</sub>	H		286 <sup>b</sup>			24.9 (7)
20	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	70	212-213	C <sub>9</sub> H <sub>9</sub> ClN <sub>3</sub> S	C, H, N, S	Inactive
21	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>		203-204 <sup>b</sup>			53.7 (9) <sup>c</sup>
22	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	78	172-173	C <sub>11</sub> H <sub>12</sub> ClN <sub>3</sub> OS	C, H, N	42.9 (9) <sup>d</sup>
23	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	80	191-193	C <sub>10</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> S	C, H, N	19.2 (5)
24	4-FC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	84	173-174	C <sub>10</sub> H <sub>10</sub> FN <sub>3</sub> S	C, H, N, S	29.1 (7)
25	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	76	182-184	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> S	C, H, S	21.9 (7)
26	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	81	155-156	C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> S	C, H, S	Inactive
27	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	76	172-174	C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> S	C, H, S	19.6 (7)
28	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>11</sub>	69	189-190	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> S	C, H, S	28.5 (7)
29	4-C <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	84	161-162	C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> S	C, H, N, S	34.4 (9) <sup>f</sup>
30	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	92	276-278	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, N, S	45.3 (9) <sup>g</sup>
31	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	84	214-216	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>	C, H, N	39.4 (9) <sup>h</sup>
32	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	92	205-206	C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, N, S	Inactive
33	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	89	191-192	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, S	Inactive
34	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	91	275 dec	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, N, S	Inactive
35	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	84	167-168	C <sub>12</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, N, S	Inactive
36	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<i>i</i> -C <sub>4</sub> H <sub>9</sub>	92	220-222	C <sub>12</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, S	23.7 (7)
37	4-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>11</sub>	81	233-235	C <sub>14</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>	C, H, N	17.7 (7)
38	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	88	228-229	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> S	C, H, N, S	27.8 (7)
39	4-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	58	246-248	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> S	C, H, N, S	Inactive

<sup>a</sup> Figures in parenthesis indicate the time in hours for this reduction. <sup>b</sup> *J. Pharm. Sci.*, **58**, 1398 (1969). <sup>c</sup> See Table I. <sup>d</sup> Reduction (26.9%) at 24 hr. <sup>e</sup> *Anal.* Calcd for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>S: C, 61.80. Found: C, 61.15. <sup>f</sup> Reduction (23.5%) at 24 hr. <sup>g</sup> See Table II. <sup>h</sup> Reduction (27.3%) at 24 hr. <sup>i</sup> *Anal.* Calcd for C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>S: N, 25.45. Found: N, 24.85.

antibacterial action against *Salmonella typhi*, *Staphylococcus aureus*, *Vibrio comma*, and *Escherichia coli*.

Acute toxicity studies showed that **21** and **30** were much less toxic than tolbutamide. The maximum tolerated single doses (oral) in albino mice for **21** and **30** were 4.0 and 5.0 g/kg, respectively, while LD<sub>50</sub> of tolbutamide (oral) was 2.6 g/kg. Chronic toxicity experiments were carried out in rats fed orally at a dose level of 100 mg/kg for more than 8 weeks. The

animals receiving **21** and **30** maintained good physical condition, showed no significant differences in weight gain as compared with controls, and no macroscopic or microscopic abnormalities were seen in the animals.

## Experimental Section

**Screening Method.**—The hypoglycemic activity was tested in normal fasting albino rats weighing 180-200 g. The drug was

administered orally as a suspension in 2% gum acacia, and blood sugar was determined at 1.5, 3, 5, 7, 9, and 24 hr by Somogyi's method<sup>1</sup> using Nelson's reagent.<sup>2</sup> The crossover tests were carried out with tolbutamide at 25 mg/kg dose level using 7 animals in each group. One group was given the test drug while the other received tolbutamide. Following a rest period of 1 week, the drugs were crossed over and the test was repeated.

For alloxan-diabetic rats, healthy male albino rats weighing about 200 g were fasted overnight and injected with an aqueous solution of alloxan monohydrate at 200 mg/kg dose level and food given immediately. Only diabetic animals were used in the rest.

**Chemical Method.**<sup>3</sup> *p*-Ethylbenzhydrazide.—Ethyl *p*-ethylbenzoate (44.5 g, 0.25 mol), N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O (25 ml of 98%) and EtOH (100 ml) were mixed and heated under reflux for 2 hr. The residue after removal of EtOH was triturated with Et<sub>2</sub>O, filtered, and washed (Et<sub>2</sub>O). It was dried (H<sub>2</sub>O), yield 39.1 g (95%), mp 89–90°. *Anal.* (C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O) C, 11.

(1) M. Somogyi, *J. Biol. Chem.*, **160**, 69 (1945).

(2) N. Nelson, *ibid.*, **153**, 375 (1944).

(3) The melting points were taken in capillary tubes with a partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within 0.4% of the theoretical values.

**1-*p*-Sulfamoylbenzoyl-4-ethylthiosemicarbazide.** *p*-Sulfamoylbenzoylhydrazide (21.5 g, 0.1 mol) was dissolved in dioxane (150 ml) and heated under reflux with ethyl isothiouracate (9.5 ml, 0.11 mol) for 4 hr. The solid that separated on cooling was collected by filtration, washed (H<sub>2</sub>O), and dried (EtOH).

All the thiosemicarbazides required for the present work were similarly prepared and dried from EtOH. See Table IV for the new thiosemicarbazides.

**5-*p*-Sulfamoylphenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol.** 1-*p*-Sulfamoylbenzoyl-4-ethylthiosemicarbazide (6.0 g, 0.02 mol) was dissolved in 2*N* NaOH (60 ml) and refluxed for 2 hr. The reaction mixture was cooled and acidified with HCl (pH 4). The white precipitate of the desired compound was filtered, washed (H<sub>2</sub>O), and dried (85% EtOH).

All the new triazoles which were prepared similarly and dried from EtOH are listed in Table V with their melting points, analytical data, etc.

**Acknowledgments.**—The authors wish to thank Shri M. T. Jaokar and coworkers for the microanalyses and to Dr. N. K. Dutta, Director, Haffkine Institute, for his interest in the work.

## Saligenin Analogs of Sympathomimetic Catecholamines<sup>1a,b</sup>

D. T. COLLIN, D. HARTLEY,<sup>1c</sup> D. JACK, L. H. C. LUNTS, J. C. PRESS, A. C. RITCHIE, AND P. TOON

*Chemistry Department, Allen and Hanburys Ltd., Ware, Hertfordshire, England*

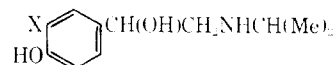
*Received February 18, 1970*

Analogs of isoproterenol have been prepared in which the catechol group has been replaced by salicylic acid (IX) or saligenin (VII) functions. Many of the latter are potent long-lasting  $\beta$ -adrenoreceptor stimulants that are effective orally and show a highly selective action on bronchial smooth muscle. Structure-activity relationships are discussed and related to current theories of molecular processes at  $\beta$ -adrenoreceptors.

Sympathomimetic amines that relax bronchial smooth muscle by stimulation of  $\beta$ -adrenoreceptors have been widely used as bronchodilators in reversible airways obstruction and extensive investigations of structure-activity relations have been made.<sup>2</sup> Maximum potency has always been associated with the presence of a catechol function as in isoproterenol (Ia). The catecholamines have only a short duration of parenteral action probably mainly owing to uptake into tissues<sup>3,4</sup> but also because of metabolism by catechol-*O*-methyl transferase (COMT) to a methyl ether, *e.g.*, Ib.<sup>5</sup> The latter is a  $\beta$ -adrenoreceptor blocker.<sup>6</sup> An additional metabolic barrier may underlie the ineffectiveness of the catecholamines when administered orally since it has been shown in the dog<sup>3</sup> and in man<sup>4</sup> that they are inactivated by conversion into an *O*-sulfate ester in the gut.

We hoped to circumvent these metabolic pathways and hence overcome some of the clinical deficiencies of

isoproterenol by the preparation of compounds of formula I where X was a group which retained some of the attributes of the catechol but which would not be subject to attack by the enzymes that inactivate the latter.



Ia. X = HO      Ic. X = MeSO<sub>2</sub>NH      Ie. X = HOCH<sub>2</sub>  
Ib. X = MeO      Id. X = HOOC

Previous replacement of one or both phenolic groups<sup>7</sup> by other substituents has drastically reduced sympathomimetic action except in the case of compounds such as Ic where the bioisosteric methanesulfonamide group produces a pseudocatechol.<sup>8</sup> The enhanced acidity of the *m*-phenolic group in the catecholamines, which is simulated by the methanesulfonamide group, is considered important for high biological activity.<sup>9</sup> An additional feature of possible importance is the ability of the catechol moiety to chelate with metals.<sup>9</sup> Both of these properties are displayed, with the minimum of steric disturbance, by the salicylic acid Id which was our first objective. A general synthetic route to Id, outlined in Scheme I, also leads to the saligenin derivative Ic which should still be capable of chelating

(1) (a) For preliminary communication of this work see D. Hartley, D. Jack, L. H. C. Lunts, and A. C. Ritchie, *Nature (London)*, **219**, 861 (1968). (b) Presented in part at the Fourth Rencontres Internationales de Chimie Thérapeutique, Clermont-Ferrand, 1968. (c) To whom inquiries should be addressed.

(2) For leading references see (a) P. Pratesi and E. Grana, *Advan. Drug Res.*, **2**, 127–142 (1965); (b) R. R. Barlow, "Introduction to Chemical Pharmacology," Methuen and Co., London, 1964, pp 282–343; (c) A. M. Lamlis and T. G. Brown in "Drugs Affecting the Peripheral Nervous System," Vol. 1, A. Burger, Ed., Dekker, New York, N. Y., 1967, p 399.

(3) W. D. Conway, H. Minatoya, A. M. Lamlis, and J. M. Shekotsky, *J. Pharm. Sci.*, **57**, 1135 (1968).

(4) D. C. Morgan, M. Sammler, D. S. Davies, M. Conolly, J. W. Paterson, and C. T. Dollery, *Biochem. J.*, **114**, 8P (1969).

(5) S. R. Ross, *Acta Pharmacol. Toxicol.*, **20**, 267 (1963).

(6) J. W. Paterson, M. E. Conolly, D. S. Davies, and C. T. Dollery, *Lancet*, **2**, 126 (1968).

(7) For leading references see R. H. Uloth, G. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).

(8) A. A. Larsen, W. A. Gould, H. R. Roth, W. T. Comer, R. H. Uloth, K. W. Dizon, and P. M. Lish, *ibid.*, **10**, 462 (1967).

(9) B. Bellegu in "Ciba Foundation Symposium on Adrenergic Mechanisms," J. R. Vane, G. E. Wulstenholme, and M. O'Connor, Eds., Churchill, London, 1969, p 233.