membrane elicited by postganglionic stimulation seem then to be due not only to a moderate inhibition at the level of the ganglionic synapses but also to a relaxing effect directly exerted by the injected substances on the smooth muscular fibers of the vascular walls and nictitating membrane.

Substituted Heteroaromatic Anthranilic Acids with Antiinflammatory Activity

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The pronounced pharmacological activities of N-(2,3-dimethylphenyl)anthranilic acid (mefenamic acid)[1] and of other substituted anthranilic acids[2,3] have stimulated other workers to prepare and evaluate numerous analogs of this class of compounds for their analgetic and antiinflammatory properties. Sutton and Birnie[4] described the synthesis of 1-carboxy-8-trifluoromethylphenothiazine, an active tricyclic sulfur analog of N-(3-trifluoromethylphenyl)anthranilic acid (flufenamic acid). Recently, series of anilinopyridinecarboxylic acids[5] and 4-anilinopyrimidine-5-carboxylic acids[6] have been prepared, and significant antiinflammatory activity has been established for several members of each group of compounds.

These results suggest that the anthranilyl ring of mefenamic acid may be subjected to considerable manipulation without seriously affecting the activity. We wish to report the synthesis and pharmacology of novel anthranilic acids containing heteroaromatic N-substituents. Only a few compounds of this type have previously been reported in the literature.[7]

Chemistry.—The majority of the compounds listed in Tables I–III were prepared by the reaction of appropriately substituted chloro heterocycles with anthranilic acid in hydrochloric acid in a manner similar to that employed by Banks[8] for the preparation of N-(substituted pyrimidinyl)anilines. Alternatively, substituted methylthio heterocycles were treated with anthranilic acid in alkaline solution (**18**, Table II, and **23**, Table III).

N-[5-(4-Carboxy-2,6-dihydroxypyrimidinyl)]anthranilic acid (**20**) was prepared under Ullmann conditions from *o*-bromobenzoic acid and 5-amino-4-carboxy-2,6-dihydroxypyrimidine.

When 2-chloro-4-diethylamino-6-methylpyrimidine and anthranilic acid were heated in dilute HCl, the dihydrochloride of the anilinium salt of **19** was isolated in 45% yield. Under the influence of the 4-diethylamino substituent of the pyrimidine ring, extensive decarboxylation of the anthranilic acid had occurred. This effect was not observed during the preparation of the related *s*-triazine derivatives under the same conditions.

With few exceptions the intermediate chloro- and methylthio heterocycles are known compounds. The preparation of the new compounds of this type by established procedures is described in the Experimental Section. A convenient and efficient method for the synthesis of 5-chloropyrimidines was developed. 5-Chloro-2,6-dimethyl-4-hydroxypyrimidine had previously been prepared by the condensation of acetamidine and ethyl α-chloroacetoacetate.[9] We obtained the compound in high yield by direct chlorination of 2,6-dimethyl-4-hydroxypyrimidine with aqueous sodium hypochlorite. 5-Chloro-4,6-dimethyl-2-hydroxypyrimidine was prepared by the same method, which appears generally applicable to hydroxypyrimidines.

Biological Activity.—The compounds were screened for their antiinflammatory and analgetic activity by the following procedures: yeast edema test in mice,[10] kaolin edema test in rats,[11] and by a modified mouse-writhing test.[12]

Groups of ten white male NMRI mice were dosed orally 30 min prior to the injection of 0.02 ml of a 2% suspension of bakers yeast into the plantar surface of the left hind paw of each animal. After 3 hr the mean per cent weight increase of the inflamed paws was compared with that obtained in the control group, and the results are expressed as per cent inhibition.

The kaolin edema was induced by injection of 0.1 ml of a 10% suspension of kaolin into the left hind paw of groups of ten male Wistar rats immediately after the oral administration of the test compound. The degree of swelling was measured volumetrically 5 hr later and the results are expressed as per cent inhibition of swelling compared to the control group. A fixed oral dose of 300 mg/kg was employed in these two procedures.

In the writhing test for analgesia groups of five male NMRI mice were injected intraperitoneally with 0.2 ml of a 0.75% aqueous acetic acid solution and the writhings for the whole group were counted during the following 20 min. A fixed oral dose of 100 mg/kg of the test compound was given 1 hr prior to the experiment and the reduction in writhings was recorded as per cent inhibition compared with the control group. If the fixed dose resulted in more than 50% inhibition, lower doses were tested, and ED_{50} values were calculated.

In the yeast edema procedure the compounds **3**, **4**, **6**, **7**, **15**, **21**, and **22** showed activities ranging from 12–36% inhibition. Similar effects could be obtained with 50–200 mg/kg of acetylsalicylic acid, while a dose of 20 mg/kg of mefenamic acid resulted in 25% inhibition. The compounds **3**, **5**, **14**, **15**, and **24** caused inhibition of the kaolin edema ranging from 23–57% corresponding to the results obtained with 10–50 mg/kg of phenylbutazone or 25–100 mg/kg of mefenamic acid. In the

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(7) (a) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1131 (1944); (b) D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 4997 (1957); (c) M. Yanai and T. Konishi, *Nippon Kagaku Zasshi*, **80**, 1181 (1959); (d) T. Ueda and J. J. Fox, *J. Med. Chem.*, **6**, 697 (1963); (e) G. N. Mahapatra and M. K. Rout, *J. Indian Chem. Soc.*, **30**, 398 (1953); **31**, 933 (1954); **34**, 653 (1957); (f) H. K. Pujari and M. K. Rout, *Ibid.*, **31**, 257 (1954); (g) M. K. Rout, *Ibid.*, **33**, 795 (1956).

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(9) E. v. Meyer, *Chem. Zentr.*, **77**, 942 (1906).

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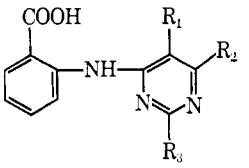
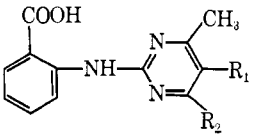
TABLE I
N-[4-(SUBSTITUTED PYRIMIDINYL)]ANTHRANILIC ACIDS



No.	R_1	R_2	R_3	Mp, °C	Crystn solvents[a]	Formula	Analyses	Antiinflam act., % inhib of edema[b] Yeast	Kaolin	Analgetic act. in mice (oral) ED_{50}, mg/kg
1	H	CH_3	CH_3	263–266	A	$C_{13}H_{13}N_3O_2 \cdot HCl \cdot 0.25H_2O$	C, H, Cl, N	0	0	>100
2	CH_3	CH_3	CH_3	>300	B	$C_{14}H_{15}N_3O_2 \cdot HCl$	C, H, Cl, N	0	0	>100
3	H	CH_3	C_6H_5	240–243	A–B	$C_{18}H_{15}N_3O_2 \cdot HCl \cdot H_2O$	C, H, Cl, N	30[c]	24[d]	>100
4	H	C_6H_5	CH_3	264–268	B–C	$C_{18}H_{15}N_3O_2 \cdot HCl$	C, H, Cl, N	28[d]	14	>100
5	H	Cl	CH_3	212–213	D–B	$C_{12}H_{10}ClN_3O_2$	C, H, Cl, N	0	57[c]	>100
6	Cl	CH_3	CH_3	263–266 dec	D–E	$C_{13}H_{12}ClN_3O_2$	C, H, Cl, N	13	19	>100
7	H	CH_3	NH_2	298–299[e,f]		$C_{12}H_{12}N_4O_2$	C, H, N	13[d]	0	>100
8	H	CH_3	$NHCH_2CH_2N(C_2H_5)_2$	229–230 dec	B–F	$C_{18}H_{25}N_5O_2 \cdot 2HCl \cdot H_2O$	C, H, N; Cl[g]	0	0	90
9	H	NH_2	SCH_3	252–257 dec	D–B–E	$C_{12}H_{12}N_4O_2S$	C, H, N, S	0	13	>100
10	H	CH_3	SCH_3	221–225	B–E	$C_{13}H_{13}N_3O_2S$	C, H, N, S	0	0	>100
11	H	C_6H_5	SCH_3	212–214	D–B–E	$C_{18}H_{15}N_3O_2S$	C, H, N, S	0	0	>100
12	Br	CH_3	SCH_3	234–237	D–B	$C_{13}H_{12}BrN_3O_2S$	C, H, Br, N, S	0	0	>100
13	Br	C_6H_5	SCH_3	256–258	D–E	$C_{18}H_{14}BrN_3O_2S$	C, H, Br, N, S	10	0	>100
14	H	CH_3	CCl_3	253–256 dec	B–G	$C_{13}H_{10}Cl_3N_3O_2$	C, H, Cl, N	0	23[c]	>100

[a] A = 0.5 *N* HCl, B = EtOH, C = Et_2O, D = DMF, E = H_2O, F = EtOAc, G = MeCN. [b] Dosage of all compounds was 300 mg/kg orally. [c] $p < 0.001$. [d] $p < 0.05$. [e] The compound was recrystallized from 3 *N* HCl and then treated with NaOH. [f] Lit.[7c] mp 286°. [g] Cl: calcd, 12.77; found, 13.34.

TABLE II
N-[2-(SUBSTITUTED PYRIMIDINYL)]ANTHRANILIC ACIDS



No.	R_1	R_2	Mp, °C	Crystn solvents[a]	Formula	Analyses	Antiinflam act., % inhib of edema[b] Yeast	Kaolin	Analgetic act. in mice (oral) ED_{50}, mg/kg
15	H	CH_3	236–237.5	D–B	$C_{13}H_{13}N_3O_2$	C, H, N	36[c]	41[c]	85
16	Cl	CH_3	223–225	D–B	$C_{13}H_{12}ClN_3O_2$	H, Cl; C,[d] N[e]	0	0	>100
17	H	C_6H_5	238–241 dec	D–B	$C_{18}H_{13}N_3O_2$	C, H, N	0	0	>100
18	H	OH	248–250 dec	D	$C_{12}H_{11}N_3O_3$	H, N; C[f]	9	0	>100
19	H	$N(C_2H_5)_2$	229–232 dec	D	$C_{16}H_{20}N_4O_2$	C, H, N	0	12	85

[a–c] See corresponding footnotes in Table I. [d] C: calcd, 56.22; found, 57.17. [e] N: calcd, 15.13; found, 15.68. [f] C: calcd, 58.77; found, 59.22.

writhing test for analgesia the most potent substances were **8**, **15**, and **19**, all with ED_{50} values of 85–90 mg/kg. The corresponding value for acetylsalicylic acid is 50–100 mg/kg.

In order to obtain a rough, qualitative measure of absorption, the urine of the orally dosed animals was routinely tested by thin layer chromatography for excretion products originating from the test compounds. Positive indication of some degree of absorption was found for all compounds, except **7**, **10**, and **13**.

From this study it appears that the exchange of the *o*-xylyl moiety in mefenamic acid with heteroaromatic rings significantly lowers the antiinflammatory activity.

Experimental Section[13,14]

Starting Materials.—The chloropyrimidines were either obtained from commercial sources or prepared after known procedures.[15] 4-Chloro-2-(2-diethylaminoethylamino)-6-methylpyrimidine,[16] 4-chloro-2-methylthio-6-phenylpyrimidine,[17] 2,4-dichloro-6-diethylamino-*s*-triazine,[18] 2-chloro-4,6-bis(diethylamino)-*s*-triazine,[18] and 5-chloro-3-methyl[1,2,4]thiadiazole[19] were prepared according to previously reported methods.

N-Heteroaromatic Anthranilic Acids (1–13, 15–17, 22, and 24).—A mixture of 0.1 mole of the appropriate chloro heterocycle, 0.1 mole of anthranilic acid, 10 ml of concentrated HCl, and 100

(13) All melting points are corrected and were determined in a capillary tube. Microanalyses were carried out by Mr. P. Hansen, Microanalytic Department, The University of Copenhagen, Copenhagen, Denmark.

(14) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(15) D. J. Brown, "The Pyrimidines," A. Weissberger, Ed., John Wiley and Sons Inc., New York, N. Y., 1962.

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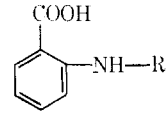
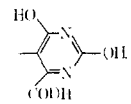
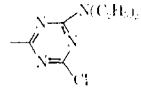
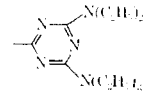
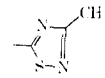
TABLE III
MISCELLANEOUS N-HETEROAROMATIC ANTHRANILIC ACIDS



No.	R	Mp, °C	Cryst solvents[a]	Formula	Analyses	Antiinflam act., % inhib of edema[b] Yeast	Kaolin	Analgetic act. in mice (orally) ED_{50}, mg/kg
20		>300[d]		$C_{12}H_9N_3O_6$	C, H, N	0	0	>100
21		184–188	B	$C_{14}H_{16}ClN_3O_2$	C, H, N, Cl	12[c]	0	>100
22		188–205 dec	B–C	$C_{18}H_{26}N_6O_2 \cdot HCl$	C, H, N, Cl	24[c]	0	>100
23		189–193 dec	D–B–E	$C_{10}H_8N_2O_3S$	C, H, N, S	11	0	>100
24		203–205 dec	D–B–E	$C_{10}H_9N_3O_2S$	C, H, N, S	0	28[c]	>100

[a,b] See corresponding footnotes in Table I. [c] $p < 0.05$. [d] The sodium salt was recrystallized from EtOH–Et_2O, dissolved in H_2O, and precipitated with acid. [e] $p < 0.01$.

ml of H_2O was refluxed for 2–4 hr. In most cases the compounds precipitated upon cooling. Otherwise the reaction mixture was evaporated to dryness. The products were recrystallized from the solvents indicated in the Tables I–III.

4-Hydroxy-6-methyl-2-trichloromethylpyrimidine.—A mixture of 67.1 g (0.416 mole) of trichloroacetamidine[20] and 54.1 g (0.416 mole) of ethyl acetoacetate was left at room temperature for 24 hr. The crystals formed were dissolved in a hot mixture of 300 ml of 3 *N* HCl and 100 ml of EtOH. The solution was rapidly cooled; yield of crude product, 49.8 g (53%), mp 105–112°. The crude product was used in the next step without further purification. When the product was recrystallized twice from chloroform–petroleum ether (bp 30–45°) and washed with cold 3 *N* HCl, an analytically pure sample was obtained, mp 177–179°. *Anal.* ($C_6H_5Cl_3N_2$) C, H, N, Cl.

N-[4-(6-Methyl-2-trichloromethylpyrimidinyl)]anthranilic Acid (14).—A mixture of 29.0 g (0.128 mole) of crude 4-hydroxy-6-methyl-2-trichloromethylpyrimidine and 120 ml of $POCl_3$ was refluxed for 20 min. Excess $POCl_3$ was removed *in vacuo* and the residue was poured on ice. The precipitate was collected and washed (H_2O). The crude 4-chloro-6-methyl-2-trichloromethylpyrimidine (19.3 g, 0.0785 mole, mp 58–61°), anthranilic acid (10.8 g, 0.0785 mole), and 75 ml of EtOH were refluxed for 10 hr. The precipitate (10.2 g, 23%, mp 248–253° dec) was recrystallized from EtOH–MeCN.

5-Chloro-2,6-dimethyl-4-hydroxypyrimidine.—To a solution of 37.7 g (0.234 mole) of 2,6-dimethyl-6-hydroxypyrimidine[15] in 200 ml of H_2O was added 450 ml of 15% aqueous NaOCl. After 1 hr at room temperature the white precipitate was collected. The filtrate was concentrated to one-third of its volume and a further crop of product was obtained. The combined crops were dissolved in hot 3 *N* AcOH. On cooling the pure compound precipitated; yield 33.2 g (90%, mp 191–193°, lit.[9] 191°). *Anal.* ($C_6H_7ClN_2O$) Cl.

5-Chloro-4,6-dimethyl-2-hydroxypyrimidine.—4,6-Dimethyl-2-hydroxypyrimidine hydrochloride[15] (20.0 g, 0.125 mole) was treated with 320 ml of 15% aqueous NaOCl yielding 13.4 g (68%), mp 238–242° dec; after two recrystallizations from H_2O, mp 241–245° dec. *Anal.* ($C_6H_7ClN_2O$) C, H, N, Cl.

2,5-Dichloro-4,6-dimethylpyrimidine.—5-Chloro-4,6-dimethyl-2-hydroxypyrimidine (27.0 g, 0.170 mole) was refluxed with 60 ml of $POCl_3$ and 20 ml of diethylaniline; yield 26.5 g (88%), mp 55–56°; after one recrystallization from 25% EtOH, mp 63–64°. *Anal.* ($C_6H_6Cl_2N_2$) C, H, N, Cl.

N-[2-(4-Hydroxy-6-methylpyrimidinyl)]anthranilic Acid (18).—A mixture of 15.0 g (0.096 mole) of 4-hydroxy-6-methyl-2-methylthiopyrimidine,[15] 13.2 g (0.096 mole) of anthranilic acid, 5.1 g (0.048 mole) of Na_2CO_3, and 150 ml of H_2O was heated to reflux for 20 hr. EtOH (75 ml) was added until a clear solution was obtained. After cooling, the precipitate (40.2 g, 82%) was collected and dissolved in 300 ml of 1 *N* NaOH and 300 ml of EtOH. The solution was treated with charcoal and acidified. The precipitate was recrystallized from DMF.

N-[2-(4-Diethylamino-6-methylpyrimidinyl)]anthranilic Acid (19).—When 2-chloro-4-diethylamino-6-methylpyrimidine[15] and anthranilic acid were treated in dilute HCl according to the general procedure the product obtained was shown to be the dihydrochloride of the anilinium salt of **19**, mp 226–230°. *Anal.* ($C_{16}H_{20}N_4O_2 \cdot C_6H_5NH_2 \cdot 2HCl$) C, H, N, Cl. This compound was dissolved in 2 *N* NaOH, and the solution was washed with ether and neutralized with 3 *N* HCl. The precipitate (**19**) was recrystallized from DMF.

N-[5-(4-Carboxy-2,6-dihydroxypyrimidinyl)]anthranilic Acid (20).—A mixture of 16.0 g (0.0935 mole) of 5-amino-4-carboxy-2,6-dihydroxypyrimidine,[15] 18.8 g (0.0935 mole) of *o*-bromobenzoic acid, 2.0 g of freshly reduced Cu powder in 125 ml of H_2O, and 12.4 g (0.0935 mole) of K_2CO_3 was refluxed for 14 hr. The reaction mixture was filtered and the filtrate was acidified with HCl. The precipitate (23.6 g, 87%) was dissolved in aqueous $NaHCO_3$ and the solution was saturated with NaCl. The precipitated sodium salt of **20** was recrystallized twice from H_2O–EtOH and then dissolved in H_2O. The solution was acidified with HCl and pure **20** precipitated.

N-[2-(4-Chloro-6-diethylamino-*s*-triazinyl)]anthranilic Acid (21).—To a solution of 12.7 g (0.0925 mole) of anthranilic acid and 4.9 g (0.0463 mole) of Na_2CO_3 in 125 ml of H_2O was added a solution of 20.4 g (0.0925 mole) of 2,4-dichloro-6-diethylamino-*s*-triazine[18] in 25 ml of EtOH. The temperature was kept at 40–45° for 6 hr. After cooling, the precipitate (20.8 g, 70%, mp 182–184°) was collected and recrystallized from EtOH.

N-[2-(4-Oxo-2-thiazolinyl)]anthranilic Acid (23).—To a solution of 40.0 g (0.30 mole) of rhodanine[21] and 12.0 g (0.30 mole) of NaOH in 575 ml of MeOH and 145 ml of H_2O was added 44.0

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g (0.31 mole) of MeI. The solution was left for 24 hr at room temperature and then concentrated to one-third the original volume. A solution of 41.2 g (0.30 mole) of anthranilic acid in 600 ml of EtOH was added. After reflux for 7 hr the precipitate (13.8 g, 20%, mp 192–196°) was collected. The filtrate was concentrated and a further crop of 11.8 g (17%) was obtained. The product was recrystallized from DMF–EtOH–H_2O.

Acknowledgments.—The skillful technical assistance of Miss L. Haugaard, Miss E. Jessen, and Mrs. V. Karll is gratefully acknowledged.

o-Acetoxyphenylacetic Acid, an Aspirin Homolog

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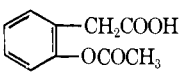
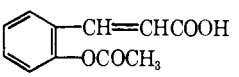
Ever since the introduction of aspirin into medicine in 1899, molecular modifications have been prepared in the hope of improving either the pharmacological or physical properties of the drug. It is of interest that the first higher homolog, *o*-acetoxyphenylacetic acid (I), has not been successfully synthesized thus far.



I

Bauer and Lasala[1] attempted the preparation but did not indicate the nature of the experiments. They did, however, prepare β-(*o*-acetoxyphenyl)propionic acid (II) and reported analgetic properties in rats (by the D'Amour and Smith method) and in rheumatic patients. It is now found, using the bradykinin-induced writhing test (in mice), that II shows no significant analgetic activity. The unsaturated analogs of II, *trans*-*o*-acetoxyphenylcinnamic (IIIa) and *cis*-*o*-acetoxyphenylcinnamic acid (IIIb) were also screened for analgetic action. IIIa showed no significant activity; IIIb, however, did, on the basis of the limited testing, show some activity (see Table I).



III

TABLE I

INHIBITION OF WRITHING

Compd	Dose, mg/kg	No. writhing/ no. tested	% inhib of writhing
Aspirin	125	11/20	45
I	135	28/30	6.5
II	145	48/59	19
IIIa	143.75	17/20	15
IIIb	143.75	13/20	35
1% Tragacanth (control)	10 ml	74/80	7.5

In view of the above it was therefore of interest to prepare I and determine its analgetic activity. Pfeiffer and Enders[2] had also unsuccessfully attempted to prepare I. Their treatment of *o*-hydroxyphenylacetic acid (IV) with acetyl chloride and pyridine resulted in benzo-2(3H)-furanone. Acetylation of IV with acetic anhydride and sodium acetate gave *o*-acetoxyphenylacetic acid anhydride (V); saponification of V with bicarbonate solution led to the rearranged 2-methyl-3-coumarincarboxylic acid (VI). Treatment of IV with acetic anhydride and pyridine gave VI directly.

Since direct acylation apparently was impossible it was decided to block the carboxyl group, acylate the phenolic function, and subsequently remove the block. *t*-Butyl (*o*-hydroxyphenyl)acetate (VII) was prepared but could not be acetylated; there resulted either recovery of starting material or decomposition. Benzyl (*o*-hydroxyphenyl)acetate (VIII) was then synthesized by transesterification of the methyl ester. Acetylation with acetic anhydride catalyzed by sulfuric acid or pyridine readily yielded benzyl (*o*-acetoxyphenyl)acetate (X). Reductive debenzylation of IX then afforded I.

Experimental Section

All melting points and boiling points are uncorrected. Melting points were determined on a Fisher-Johns apparatus. Ir spectra were obtained from KBr pellets with a Perkin-Elmer Model 337 instrument. Elemental analyses and analgetic testing were done by Smith Kline and French Laboratories. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

o-Coumaric acid was prepared in 75–80% yield from coumarin by treatment with aqueous NaOH and yellow HgO by the procedure of Seshardi and Rao.[3] Acetylation according to Schultz[4] afforded IIIa in 96% yield. Reduction of IIIa according to Bauer and Lasala[1] gave II in 79% yield. The preparation of IIIb was accomplished in 47.5% yield according to Stoermer and Ladewig[5] by saponification of coumarin with NaOH followed by acetylation of the sodium salt of coumarinic acid (not isolated) in the cold.

***t*-Butyl (*o*-Hydroxyphenyl)acetate (VII).**—A mixture of 76 g (0.5 mole) of IV,[6] 84 g (1.5 moles) of isobutylene (liquefied in Dry Ice), and 4 ml of H_2SO_4 (98%) was shaken in a Parr hydrogenator at room temperature for 7 hr. After pouring the mixture into a suspension of 100 g of $KHCO_3$, 200 ml of H_2O, and 250 g of ice, extracting with ether, and drying (Na_2SO_4), there was obtained, on removal of solvent, 33.0 g (31.8%) of VII: bp 110–115° (2 mm); $n^{20}D$ 1.5140; d^{24}_{24} 1.0787; molecular refractivity (calcd, 52.33); $FeCl_3$ test (phenolic OH), negative; ir spectrum, as expected.

Attempted acetylations of VII failed. Thus, solution in an equivalent volume of aqueous NaOH followed by treatment with Ac_2O in the cold resulted in recovery of starting material. Treatment with Ac_2O and NaOAc at reflux afforded a product, mp 115–118°, identified as V.[2] Reaction with AcOH and *p*-toluenesulfonyl chloride in the presence of pyridine at 0° gave an intractable dark oil.

Benzyl (*o*-Hydroxyphenyl)acetate (VIII).—Methyl (*o*-hydroxyphenyl)acetate (IX) was prepared in 96% yields by refluxing IV in excess anhydrous MeOH with HCl gas or *p*-toluenesulfonic acid, mp 69–71° (lit.[7] mp 73°). A mixture of 61.6 g (0.372 mole) of IX and 150 ml of freshly distilled benzyl alcohol, in which

(1) C. W. Bauer and E. F. Lasala, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 48 (1960).

(2) P. Pfeiffer and E. Enders, *Chem. Ber.*, **84**, 247 (1951).

(3) T. S. Seshardi and P. S. Rao, *Proc. Indian Acad. Sci.*, **3A**, 293 (1936).

(4) H. W. Schultz, *J. Pharm. Sci.*, **52**, 503 (1963).

(5) R. Stoermer and B. Ladewig, *Chem. Ber.*, **44**, 651 (1911).

(6) Obtained from K and K Laboratories, Plainview, N. Y.

(7) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.