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.

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o-Acetoxyphenylacetic Acid, an Aspirin Homolog

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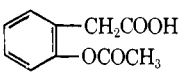
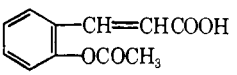
Ever since the introduction of aspirin into medicine in 1899, molecular modifications have been prepared in the hope of improving either the pharmacological or physical properties of the drug. It is of interest that the first higher homolog, *o*-acetoxyphenylacetic acid (I), has not been successfully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

0.23 g of Na had been dissolved, was heated in an open Berzelius beaker at 130–140° for 16 hr. The solid, precipitating on cooling, was filtered off. The crude product (63.5 g) was dissolved in boiling EtOH (90%) and acidified with HCl and the slight precipitate that formed was filtered off. The solvent was removed and the residue was crystallized from cyclohexane; mp 98–100°, yield 45.0 g (48%). *Anal.* ($C_{15}H_{14}O_3$) C, H. Ir absorption bands were as expected.

Benzyl (*o*-Acetoxyphenyl)acetate (X).—A mixture of 24.2 g (0.1 mole) of VIII, 50 ml of Ac_2O, and 3 ml of pyridine (or 1.5 ml of H_2SO_4) was heated on a water bath for 2–3 hr. After pouring into ice water, the oily layer was separated and diluted (Et_2O). The ether solution was washed twice with saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue gave 22.9 g (80%) of product: bp 168–172° (0.4 mm); $n^{26.5}D$ 1.5425; d^{37}_4 1.132; $FeCl_3$ test (phenolic OH), negative. *Anal.* ($C_{17}H_{16}O_4$) C, H. Ir absorption bands were as expected.

***o*-Acetoxyphenylacetic Acid (I).**—A solution of 22.9 g (0.0806 mole) of X in 100 ml of anhydrous MeOH was hydrogenated over 1 g of 5% Pd–C at room temperature at an initial pressure of 4.2 kg/cm² for 2 hr. Filtration of the catalyst followed by removal of the solvent *in vacuo* yielded a viscous oil which crystallized on refrigeration overnight; yield 13.0 g (83%). A sample recrystallized twice from C_6H_6–cyclohexane melted at 62–63°; λ_{max} 5.68 (acetoxy C=O), 5.88 (carboxyl C=O), 8.10 (ester C–O–C), 3.2–3.45 μ (COOH). *Anal.* ($C_{10}H_{10}O_4$) C, H, neut equiv.

Pharmacological Data.—Carworth Farms male, CF-1 strain mice, weighing 13–18 g were dosed orally with the ED_{50} dose of aspirin or an equivalent dose of the other compounds on a molecular weight basis. Control groups received 1% tragacanth, 10 ml/kg. Ten mice per group were used and six groups served as controls.

Twenty minutes after dosing, the animals were given a 0.2-ml ip injection of bradykinin (Sandoz) diluted to 100 μg/ml with triply distilled deionized H_2O. Fifteen minutes later the animals were reinjected with 0.1 ml and observed for writhing for a period of 20 min. The results are summarized in Table I.

Discussion

The biological data available here are somewhat puzzling. Bauer and Lasala[1] state that theoretically the most promising homologous series is the one in which the aspirin molecule is altered in the aliphatic acid side chain rather than in the acyl moiety. Their results with II apparently support this claim. In fact, their results with the D'Amour–Smith method appear to show a greater activity for II than for aspirin. The bradykinin-writhing method, however, fails to show any significant activity. It is also interesting that the vinylog IIIa shows no activity. Even though Bauer and Lasala[1] prepared this compound as an intermediate they did not test it and therefore a comparison of methods cannot be made. The *cis* isomer IIIb appears to have some activity, based on the limited screening tests reported here. Compound I proved quite inactive by the bradykinin method. The question now arises whether the two methods used for analgetic screening are equally useful, at least with aspirin analogs. Perhaps a reevaluation of the comparative results obtainable with these two methods for salicylate-type analgetics is needed.

Acknowledgment.—The author wishes to express his gratitude to Menley and James Laboratories for their financial support and especially to Dr. Kenneth R. Heimlich of Smith Kline and French Laboratories for his personal help and interest in the project. Thanks are also due to Dr. James A. Mills for the infrared spectra.

2,6-Dialkylpiperazines. V.[1] Synthesis of 2,6-Alkylpiperazine Derivatives Structurally Related to Cinnarazine

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In the first paper of this series[3] a four-step synthesis of *cis*-2,6-dimethylpiperazine (Ia) was reported. We have now found that the procedure summarized in Chart I can be extended to the synthesis of different 2,6-substituted piperazines (I) starting from a given $RR'C(NH_2)COOC_2H_5$ (IIb and c) and N-benzyl-α-bromopropionamide (IIIa). 2-Isopropyl-6-methylpiperazine (Ib) and 2,2,6-trimethylpiperazine (Ic) were thus synthesized. The use of N-benzyl-α-bromoanides different from IIIa, used in the earlier synthesis of I, was unsuccessful in the two cases examined. N-Benzyl-α-bromoisovaleramide (IIIb) condensed with valine ethyl ester (IIb), but the corresponding ethyl ester benzylamide IVb when heated at 250–260° formed resinous material from which Vb was not isolated; N-benzyl-α-bromoisobutyramide (IIIc) failed to condense with ethyl α-aminoisobutyrate (IIc).

Availability of Ia–c prompted us to investigate the pharmacological properties of compounds in which the piperazine nucleus was replaced by these derivatives. 1-Cinnamyl-4-benzhydrylpiperazine (cinnarazine), active as an antihistaminic agent,[4] was chosen as model compound. We synthesized 1-cinnamyl-4-benzhydryl-2,6-substituted piperazines (VIIIa–c) through the pathway summarized in Chart I. Refluxing of Ia–c with an equimolar amount of benzhydryl chloride and triethylamine in toluene led to the 4-benzhydryl derivative (VIIa–c). The structure of VIIa–c was proved by an unambigous synthesis. Acylation of VIa with propionic anhydride gave 1-propionyl-4-benzyl-2,6-dimethylpiperazine (XIa) which was catalytically debenzylated to 1-propionyl-2,6-dimethylpiperazine (Xa). Condensation of Xa with benzhydryl chloride led to 1-propionyl-4-benzhydryl-2,6-dimethylpiperazine (XIa), which was found identical (mixture melting point and ir spectra) with the product obtained by propionylation of VIIa. Efforts to obtain VIIa by acid hydrolysis of XIa led to isolation of a mixture of starting compound and 1-propionyl derivate Xa, caused apparently by a preferential cleavage of the N-benzhydryl bond. Finally, condensation of VIIa–c with cinnamyl chloride in refluxing toluene and in the presence of an equimolar amount of triethylamine led to the desired compounds. We were also interested in synthesizing 1-benzhydryl-4-cinnamyl-2,6-substituted piperazines, isomers of VIIIa–c, in order to define the influence of the reversal of the substituents in the 1 and 4 position on the pharmacological activity. Any effort to introduce the bulky benzhydryl group in the N^1 position of the 2,6-substituted piperazine nucleus by treating benzhydryl halides

(1) Paper IV: G. Cignarella and E. Testa, *J. Med. Chem.*, **11**, 592 (1968).
(2) To whom inquiries should be addressed.
(3) G. Cignarella, *J. Med. Chem.*, **7**, 241 (1964).
(4) B. N. Halpern, C. Stiffel, M. Liacopoulos-Briot, and L. Conovici, *Arch. Intern. Pharmacodyn.*, **142**, 170 (1963).