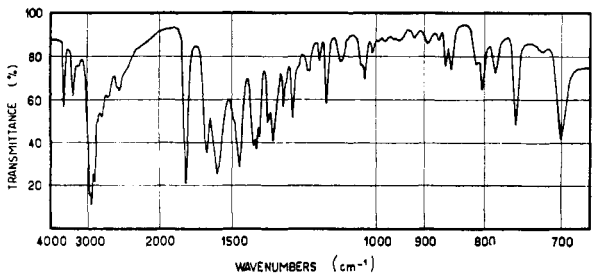

Figure 1

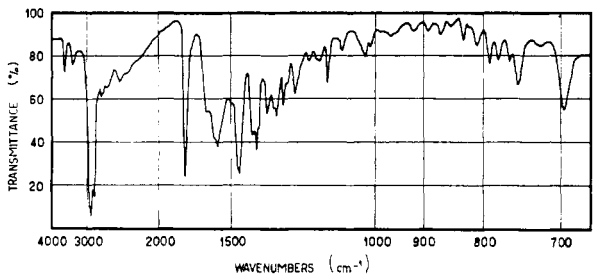

Figure 2

tallization of its dibenzylethylenediamine salts. The substitution of the amino group on a β-lactam ring with a hydroxy group is likely to decrease further the stability of 6-APA, so that it was quite impossible for us to isolate any amount of compound Ic.

Acids Ia and Ib are useful starting compounds for further investigations on the 6-APA chemical behavior. Ia and Ib, in the form of their dibenzylethylenediamine (DED) salts, are devoid of microbiological activity against *M. pyogenes aureus* 209 P [m.i.c./γ ml.: Penicillin G = 0.05; 6-APA = 5; Ia (DED − salt) > 100; IIa (DED − salt) > 100].

Experimental

6-Chloropenicillanic Acid (Ia).—A solution of 6.5 g. of 6-APA in 100 ml. of 1 *N* hydrochloric acid was cooled to 0–2° and a solution of 2.5 g. of sodium nitrite in 20 ml. of water was added dropwise. One hour after the completion of the addition, the temperature was allowed to rise to 15–18° and the separated oil extracted with ethyl ether. The organic layer was dried over sodium sulfate and the ether evaporated *in vacuo* at room temperature. The oily residue, 4.5 g., showed in the infrared spectrum bands at 1725 cm.$^{-1}$ (C=O stretching of carboxylic group) and at 1770 cm.$^{-1}$ (C=O stretching of β-lactam fused to thiazolidine ring) in agreement with the structure of Ia.

This oil, which decomposed under distillation, was dissolved in ethyl ether and treated with an ether solution of dibenzylethylenediamine; 5.5 g. of Ia dibenzylethylenediamine salt was obtained, which, after several crystallizations from aqueous ethanol, melted at 159–160°; $[\alpha]_D$ +154.4 (*c* 0.5%, in methanol). The infrared spectrum is reported in Fig. 1.

Anal. Calcd. for $C_{32}H_{40}Cl_2N_4O_6S_2$: C, 54.00; H, 5.67; N, 7.88; S, 9.01; Cl, 9.97. Found: C, 53.75; H, 6.19; N, 7.65; S, 8.99; Cl, 10.24.

6-Bromopenicillanic Acid (Ib).—was prepared essentially in the same way described for Ia, starting from 4.32 g. of 6-APA dissolved in 50 ml. of 2.5 *N* sulfuric acid containing 10.4 g. of sodium bromide and adding dropwise a solution of 2.12 g. of sodium nitrite in 10 ml. of water. The oily residue (4.88 g.) showed infrared bands at 1770 and 1725 cm.$^{-1}$, confirming for Ib the supposed structure. On treatment of Ib with an ether solution of dibenzylethylenediamine, 3.4 g. of crude Ib dibenzylethylendiamine salt was obtained, which, recrystallized from aqueous ethanol, melted at 164–165°; $[\alpha]_D$ +140.9 (*c* 0.5%, in methanol). The infrared spectrum is reported in Fig. 2.

Anal. Calcd. for $C_{32}H_{40}Br_2N_4O_6S_2$: C, 48.00; H, 5.03; N, 6.99; S, 8.00; Br, 19.96. Found: C, 48.17; H, 5.11; N, 7.28; S, 7.85; Br, 19.90.

Acknowledgment.—We wish to thank Dr. M. T. Timbal for the microbiological data, Dr. G. G. Gallo and Dr. C. R. Pasqualucci for the infrared spectra and their interpretation, Dr. G. Pelizza and Mr. Restelli for the functional and elementary analyses. Dr. Anita Wittgens gave us much appreciated help in the preparation of the manuscript.

Alkylfluorophenylcarbinols with Choleretic Activity

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p-Tolylmethylcarbinol, a component of the essential oil of *Curcuma domestica*, is known to show potent choleretic activity,[1] and the same properties have been found in several of its homologs[2] and in similar heterocyclic carbinols.[3] It is also known that methyl groups can be replaced by halogens without qualitatively affecting pharmacological activity. Hence, it was of interest to investigate whether alkylfluorophenylcarbinols would likewise display choleretic activity; fluorine radicals were preferred to other halogens since the solidity of the C—F bonds in aromatic molecules renders biochemical dehalogenation more difficult. We now report the preparation, for biological evaluation, of a wide series of such fluorinated carbinols, by reaction of the appropriate alkylmagnesium bromide or iodide with *o*-, *m*-, and *p*-fluorobenzaldehyde; in this series, only methyl-*p*-fluorophenylcarbinol was known.[4] All the carbinols thus obtained in 80–90% yield, were colorless oils with an aromatic odor that was pronounced for the lower terms and less marked for the higher terms. Several arylalkyl-

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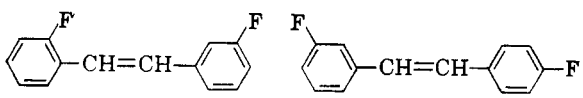
TABLE I

Carbinol	B.p., °C./mm.	n_D	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl-*p*-fluorophenyl	116/17	1.5004/28°	$C_9H_{11}FO$	70.1	70.0	7.1	7.0
Propyl-*o*-fluorophenyl	124/17	1.4958/28°	$C_{10}H_{13}FO$	71.4	71.1	7.7	7.7
Isopropyl-*p*-fluorophenyl	115/17	1.4963/28°	$C_{10}H_{13}FO$	71.4	71.1	7.7	7.8
Butyl-*p*-fluorophenyl	132/17	1.4901/21.5°	$C_{11}H_{15}FO$	72.5	72.3	8.2	8.4
Isobutyl-*p*-fluorophenyl	128/17	1.4938/28°	$C_{11}H_{15}FO$	72.5	72.2	8.2	8.5
Amyl-*p*-fluorophenyl	148/17	1.4953/19°	$C_{12}H_{17}FO$	73.5	73.4	8.7	8.7
Isoamyl-*p*-fluorophenyl	143/17	1.4937/24°	$C_{12}H_{17}FO$	73.5	73.3	8.7	8.6
Isohexyl-*p*-fluorophenyl	149/17	1.4862/26.5°	$C_{13}H_{19}FO$	74.3	74.0	9.0	9.0
β-Phenethyl-*p*-fluorophenyl	177/15	1.5732/24°	$C_{15}H_{15}FO$	78.3	78.5	6.5	6.8
γ-Phenylpropyl-*p*-fluorophenyl	185/15	1.5637/25°	$C_{16}H_{17}FO$	78.7	78.6	7.0	7.3
Ethyl-*m*-fluorophenyl	115/17	1.5039/25°	$C_9H_{11}FO$	70.1	70.0	7.1	7.0
Butyl-*m*-fluorophenyl	131/17	1.4975/25°	$C_{11}H_{15}FO$	76.5	76.2	8.2	8.3
Isohexyl-*m*-fluorophenyl	149/17	1.4913/25°	$C_{13}H_{19}FO$	74.3	74.0	9.0	9.2
Octyl-*m*-fluorophenyl	176/17	1.4830/25°	$C_{15}H_{23}FO$	75.6	75.5	9.6	9.5
Dodecyl-*m*-fluorophenyl	214/17	1.4753/24°	$C_{19}H_{31}FO$	77.6	77.3	10.5	10.8
γ-Phenylpropyl-*m*-fluorophenyl	188/17	1.5649/25°	$C_{16}H_{17}FO$	78.7	78.9	7.0	7.3
Methyl-*o*-fluorophenyl	105/17	1.5087/25°	C_8H_9FO	68.6	68.5	6.4	6.6
Propyl-*o*-fluorophenyl	118/16	1.5013/25°	$C_{10}H_{13}FO$	71.4	71.2	7.7	7.9
Amyl-*o*-fluorophenyl	144/16	...	$C_{12}H_{17}FO$	73.5	73.4	8.7	8.7
β-Phenethyl-*o*-fluorophenyl	177/15	1.5730/25°	$C_{15}H_{15}FO$	78.3	78.5	6.5	6.7

fluorophenylcarbinols, prepared from arylalkylmagnesium chlorides, were also included in our investigation. The carbinols readily underwent dehydration by means of formic acid to give the corresponding ethylenes, including the hitherto unknown 2,3′-difluorostilbene (I) and 3,4′-difluorostilbene (II).



I

II

In biological tests in rats, the lower terms of the series of carbinols reported herein displayed pronounced choleretic activity.

Experimental

Preparation of Intermediates.—*o*-, *m*-, and *p*-fluorobenzaldehyde were prepared by the Sommelet reaction from the corresponding fluorobenzyl bromides, themselves obtained from *o*-, *m*-, and *p*-fluorotoluene by side-chain bromination with *N*-bromosuccinimide in the presence of benzoyl peroxide.

Grignard Reactions.—An ethereal solution of a Grignard reagent prepared from the appropriate alkyl iodide or bromide (1.15 moles) was treated portionwise at 0° with the aldehyde (1 mole, dissolved in anhydrous ether). The mixture was refluxed for a few minutes on the water bath, and after cooling, treated with an ice-cold aqueous solution of ammonium chloride. The organic layer was then collected, washed with water, and dried over sodium sulfate, the ether was distilled, and the residue vacuum-fractionated twice. The carbinols thus obtained in 80–90% yield as colorless liquids, are listed in the table.

Dehydration of the Carbinols.—A solution of one part of the carbinol in 5 parts of anhydrous formic acid was heated for 1 hr. on the water bath. The reaction product was poured into water, taken up in benzene, and dried over sodium sulfate, the solvent was removed, and the residue vacuum-fractionated.

1-Fluorophenyl-1-propene, obtained from ethyl-*p*-fluorophenylcarbinol, was a colorless fluid liquid, b.p. 99°/17 mm., $n^{14}D$ 1.5690.

Anal. Calcd. for C_9H_9F: C, 79.4; H, 6.6. Found: C, 79.6; H, 6.6.

2,3′-Difluorostilbene (I). ***o*-Fluorobenzyl-*m*-fluorophenylcarbinol**, prepared from *o*-fluorobenzylmagnesium chloride and *m*-fluorobenzaldehyde, was a pale yellow oil, b.p. 164°/15 mm.; this underwent dehydration to the **stilbene** (I), which crystallized from pentane in colorless needles, m.p. 43°.

Anal. Calcd. for $C_{14}H_{10}F_2$: C, 77.8; H, 4.6. Found: C, 77.7; H, 4.7.

3,4′-Difluorostilbene (II). ***p*-Fluorobenzyl-*m*-fluorophenylcarbinol**, prepared as above from *p*-fluorobenzylmagnesium chloride, gave on dehydration the *stilbene* (II) which crystallized from hexane in colorless prisms, m.p. 99°.

Anal. Calcd. for $C_{14}H_{10}F_2$: C, 77.8; H, 4.6. Found: C, 77.5; H, 4.6.

Insect Sex Attractants. III. The Optical Resolution of *dl*-10-Acetoxy-*cis*-7-hexadecen-1-ol

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The extremely potent sex attractant secreted by the female gypsy moth (*Porthetria dispar*) to lure the male has been identified previously as dextrorotatory 10-acetoxy-*cis*-7-hexadecen-1-ol (I), and the equally attractive optically inactive (*dl*-) form has been synthesized.[1] The *dl*-form has now been successfully resolved by treating its acid succinate with L-brucine, separating the brucine salts by fractional crystallization from acetone, decomposing the salts, and saponifying the acid succinates with ethanolic alkali. The resulting *d*- and *l*-forms of I were identical in all respects save optical activity with one another, with the *dl*-form, and with the

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