Table III. Substituted Indole-3-acetates

Substituents	Method	Yield, %	M.P., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2,4,5,6-Tetramethyl-	D	75	136–138	$C_{16}H_{21}NO_2$	5.40	5.55
2,4,5,7-Tetramethyl-	D	52	151.5–153[a]	$C_{16}H_{21}NO_2$	5.40	5.33
2,4,6,7-Tetramethyl-	C	..	149(d.)	$C_{16}H_{21}NO_2$	5.40	5.36
2,5,6,7-Tetramethyl-	D	35	121.5–122.5	$C_{16}H_{21}NO_2$	5.40	5.30
2,4,5,6,7-Pentamethyl-	C	..	175–176(d.)	$C_{17}H_{23}NO_2$	5.12	5.07

[a] The ester should not be introduced into the m.p. apparatus until the temperature is within 5 to 10° of its m.p. The rate of heating must not exceed 1° per minute.

Table IV. Substituted Indole-3-acetic Acids

Substituents	Method	Reflux Time, Hrs.	Yield, %	M.P., °C.	Recrystallized from	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2, 4, 5, 6-Tetramethyl	E	2	60	194(d.)	acetone	$C_{14}H_{17}NO_2$	6.06	6.04
2, 4, 5, 7-Tetramethyl	E	6	98	168(d.)	dil. base	$C_{14}H_{17}NO_2$	6.06	6.18
2, 4, 6, 7-Tetramethyl	F	4.5	23[a]	168(d.)	none[b]	$C_{14}H_{17}NO_2$	6.06	6.07
2, 5, 6, 7-Tetramethyl	E	6	63	162–163(d.)[c]	none	$C_{14}H_{17}NO_2$	6.06	6.15
2, 4, 5, 6, 7-Pentamethyl	F	5	5[a]	191(d.)	methanol-water	$C_{13}H_{15}NO_2$	5.71	5.52

[a] Yield based on starting substituted indole. [b] Attempts to recrystallize the acid from organic solvents or to purify it by base-acid treatment resulted in a darkening of the color of the acid and a decrease in its decomposition point. [c] The acid should not be introduced into the melting point apparatus until the temperature is within 5 to 10° of the m.p. of the acid. The rate of heating must not exceed 1° per minute.

poured into water, and the resulting solution was extracted with ether. Addition of 3*N* hydrochloric acid to the cooled hydrolyzate precipitated the indole acids. Results are shown in Table IV.

METHOD F. This method was employed for the hydrolysis of those substituted indole-3-acetates obtained from the corresponding indoles by treatment with ethyl diazoacetate. The distillate from Method C (containing the substituted indole-3-acetate and the unreacted substituted indole) was heated under reflux with aqueous potassium hydroxide. The mixture was filtered (unreacted substituted indole recovered) and the filtrate treated as described in Method E. Results are shown in Table IV.

Preparation of 2,3,4-Trimethylnitrobenzene. The 2,3,4-trimethylnitrobenzene needed to prepare 2,3,4-trimethylphenylhydrazinium chloride is previously unreported. 1,2,3-Trimethylbenzene was nitrated with a mixture of acetic acid, acetic anhydride, and fuming nitric acid (*10*). A 40% yield of the nitro compound was obtained. Reduction, followed by acetylation, gave a compound with m.p., 140° C. The reported m.p. for 2,3,4-trimethylacetanilide is 140° C. (*3*). The boiling point of the 2,3,4-trimethylnitrobenzene at 26 mm. was 156 to 161° C.; $N_d^{28.5}$ 1.5497; d^{29} 1.1226; M.R. calcd. 46.75; M.R. exp. 46.86. Anal. calcd. for $C_9H_{11}NO_2$; N, 8.47. Found: N, 8.45.

LITERATURE CITED

(1) Allen, C.H., van Allan, J., *Org. Syn.* **22**, 94 (1942).
(2) Barclay, B.M., Campbell, N., *J. Chem. Soc.* **1945**, p. 531.
(3) Barclay, M.G., Buravoy, A., Thomson, G.H., *Ibid.*, **1944**, p. 109.
(4) Bullock, M.W., Hand, J.J., *J. Am. Chem. Soc.* **78**, 5852 (1956).
(5) Foster, R.J., McRae, D.H., Bonner, J., *Proc. Natl. Acad. Sci. U.S.* **38**, 1014 (1952).
(6) Jackson, R.W., Manske, R.H., *Can. J. Res.* **13B**, 170 (1935).
(7) Kogl, F., Kostermans, D., *Z. Physiol. Chem.* **235**, 201 (1935).
(8) Muir, R.M., Hansch, C.H., Gallup, A.H., *Plant Physiol.* **24**, 359 (1949).
(9) Piper, J.R., Ph.D. dissertation, Auburn University, Auburn, Ala., 1960.
(10) Powell, G., Johnson, F.R., *Org. Syn.* **11**, 449 (1955).
(11) Stevens, F.J., Fox, S.W., *J. Am. Chem. Soc.* **70**, 2263 (1948).
(12) Stevens, F.J., Higginbotham, *Ibid.*, **76**, 2206 (1954).
(13) Stevens, F.J., Su, H.C., *J. Org. Chem.* **27**, 500 (1962).

RECEIVED for review April 13, 1964. Accepted September 14, 1964.

Cis-Trans Isomers of Methyl Substituted Fluorocinnamic and 5-(*o*-, *m*-, and *p*-Fluorophenyl)pentadienoic Acids

RICHARD H. WILEY and H. C. VAN DER PLAS
Department of Chemistry, University of Louisville, Louisville, Ky.

INTEREST in the hypocholesterolemic activity of the geometrical isomers of 3-methyl-5-phenyl-2,4-pentadienoic acid prompted the preparation of a series of fluorophenyl analogs which are described in Table I. The trans isomers were isolated, sometimes from mixtures with other isomers, from the dehydration of the Reformatsky product. The cis isomers were obtained from UV irradiation of the trans isomers or from the β-methylglutaconic acid condensations and decarboxylations. All of the compounds listed in Table I, except those for which the NMR data are aster-

Table I. Cis-Trans Isomers of Methyl Substituted Fluorocinnamic and 5-(o-, m-, and p-Fluorophenyl)pentadienoic Acids

Compound[a]	MP, °C.	Analysis[b] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	UV[c]	NMR[d] C2H	NMR[d] $C3CH_3$
$ArCH=CHCOCH_3$								
o-F	42	73.15	72.92	5.52	5.39	...	...	...
m-F	75[e]	...	73.21	...	5.60	...	...	...
p-F	70[f]	...	73.28	...	5.51	...	...	...
$ArCH=CHCOCH=CHCOAr$								
m-F	95	75.54	75.31	4.47	4.34	...	...	...
p-F	151	...	75.58	...	4.55	...	...	...
$ArC(CH_3)=CHCO_2H$								
o-F (C)	134	66.65	66.78	5.03	5.10	235/3.8	4.17	7.87
m-F (C)	104	...	66.87	...	5.33	237/3.8	4.24	7.89
p-F (C)	119	...	66.86	...	5.27	247/3.8	3.89*	7.87P
o-F (T)	101	...	66.80	...	5.18	249/4.1	3.72P	7.33P/7.55*
m-F (T)	133	...	66.64	...	5.00	258/4.2	3.54P	7.31P
p-F (T)	144	...	66.80	...	5.10	263/4.2	3.65P*	7.33P
$ArC(=CH_2)CH_2CO_2H$								
m-F	45	66.65	66.66	5.03	5.13	241/4.0	6.60(CH_2)	4.84/4.57(:CH_2)
p-F	67	...	66.36	...	4.96	241/4.0	6.60(CH_2)	4.87/4.63(:CH_2)
$ArCH=C(CH_3)CO_2H$								
o-F (C)	115	66.65	66.38	5.03	5.29	249/4.0	7.89Me	3.38H
o-F (T)	84	...	66.30	...	4.99	257/4.2	7.98Me	2.28H
$PhC(OH)(CF_3)CH_2CO_2H$	133	51.20	51.21	3.82	3.97	...	...	...
$PhC(CF_3)=CHCO_2H$(C)	94	55.56	55.65	3.26	3.18	242/3.5	3.57*	...
$ArCH=CHC(CH_3)=CHCO_2H$								
m-F(2T4T)	161	69.89	70.21	5.37	5.50	306/4.5[g]	...	7.44P
p-F(2T4T)	195	...	70.22	...	5.36	306/4.5[g]	...	7.46P
o-F(2C4T)	180	...	69.85	...	5.32	308/4.5[g]	3.93P	7.96P
m-F(2C4T)	171	...	69.78	...	5.39	307/4.5[g]	...	7.95P
p-F(2C4T)	175	...	69.96	...	5.34	307/4.3	3.91P	7.95P
$ArCH=CHC(CH_3)=CHCO_2CH_3$								
o-F(2T4T)	58	70.89	70.79	5.95	5.82	...	4.24	7.64
p-F(2T4T)	78	...	71.04	...	5.96	...	4.26	7.66
$ArCH=C(CO_2H)C(CH_3)=CHCO_2H$								
o-F(2C4C)	206	62.38	62.39	4.43	4.44	270/4.1	...	7.89P
m-F(2C4C)	192	...	62.28	...	4.53	271/4.2	...	7.85P
p-F(2C4C)	177	...	62.28	...	4.46	275/4.2	...	7.86P

[a] The compounds were prepared by adaptations of techniques described in previous papers (*1–3*) from our laboratories; C indicates the cis and T the trans isomer. [b] Analyses by Micro-Tech Laboratories. [c] Ultraviolet absorption maxima in spectrograde methanol (0.003*N* in sulfuric acid); Beckman DK-3; mμ/log ε. [d] NMR maxima determined in carbon tetrachloride (or pyridine if marked with P) on a Varian HR-4302 60 mc. Spectrometer. Tau values in p.p.m. down field from tetramethylsilane(= 10), C2H, proton on carbon two of chain; $C3CH_3$, protons on 3-methyl; exceptions as indicated for 2-methylene structures. Asterisked values are from mixtures of cis-trans isomers. [e] B.p. at 0.25 mm. [f] B.p. at 0.07 mm. [g] Additional maxima at 228–229 mμ/log ε 4.0–4.1.

isked, are stereochemically pure as determined by NMR absorption characteristics. Other isomers were sometimes observed in mixtures. As previously noted (*1–3*), the NMR data provide unequivocal bases for cis-trans structural assignments and evidence of stereochemical purity. The preparational procedures used were similar to those previously described (*1–3*).

ACKNOWLEDGMENT

The authors gratefully acknowledge grants in support of various phases of this program from the Mead Johnson Company, the Atomic Energy Commission, and the National Institutes of Health, and a Fulbright Travel Grant (for H.C. van der Plas) in support of a post-doctoral appointment. The authors are indebted to N.F. Bray for assistance with the NMR measurements.

LITERATURE CITED

(1) Wiley, R.H., *J. Chem. Soc.* **1958**, 3831.
(2) Wiley, R.H., Crawford, T.H., Staples, C.E., *J. Org. Chem.* **27**, 1535 (1962).
(3) Wiley, R.H., van der Plas, H.C., Bray, N.F., *Ibid.*, **27**, 1989 (1962).

RECEIVED for review July 24, 1964. Accepted October 7, 1964.