cant antispasmodic action *in vitro*. With the exception of XVIII, XXI, and XXXII, all the compounds possessed only a slight analgesic action.

The most interesting feature revealed during this investigation is the marked antiinflammatory activity shown by both series. The α,α-disubstituted 1-naphthylacetamides in particular seem to be very active and worthy of more detailed study. Another point of interest is the diuretic action, as it is concurrent with the antiinflammatory activity. Here also, the naphthalene derivatives appear to be more potent than the corresponding benzene compounds. Both series cause CNS depression in mice and the symptomatology of these effects is rather similar. All the tested compounds show only slight analgesic action, although this is more pronounced for the α,α-disubstituted phenylacetamides. The naphthalene derivatives appear to be more active as local anesthetics, the most interesting of these being some amides with a piperidinoethyl or morpholinoethyl group in the α-position. A number of compounds of both series possess antispasmodic activity, but this requires further experimental study for a more accurate evaluation. Finally, the benzene derivatives generally appear to be less toxic than the corresponding naphthalene compounds.

Of all the tested substances, α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide was submitted, in the light of its interesting pharmacological pattern, to a more detailed pharmacological and toxicological investigation.[9] This substance is now undergoing clinical trials as an antiinflammatory agent.

From the point of view of the general pharmacological picture, the naphthalene derivatives seem to be more interesting than the corresponding benzene compounds.

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(9) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964).

Nonsteroidal Antiinflammatory Agents. Some Arylacetic Acids

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A series of arylacetic acids which exhibit antiinflammatory activity are described. The principal members of the series are derivatives of 1-naphthaleneacetic acid, and structure–activity relationships are discussed, particularly with regard to antiultraviolet erythema activity. Substituents on the α-carbon atom of 1-naphthaleneacetic acid exert a pronounced influence on antiinflammatory activity. Alkyl group substitution normally results in a loss of antiinflammatory activity, while unsaturated groups as exemplified by furfuryl and benzyl retain or enhance the antiinflammatory activity of 1-naphthaleneacetic acid. The biological results are discussed with reference to the established antirheumatic agent, phenylbutazone, and compared with the new antiinflammatory arylacetic acid derivatives ibufenac and indomethacin.

During the last few years several reports have appeared concerning new drugs of potential value for the symptomatic treatment of rheumatoid arthritis and similar inflammatory conditions of connective tissue. Notable among these newer drugs are the N-arylanthranilic acid derivatives, mefenamic acid[1] and flufenamic acid,[2] and the arylacetic acids, indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid][3] and ibufenac (4-isobutylphenylacetic acid).[4]

In this report a novel series of arylacetic acids are described which also have demonstrated antiinflammatory activity.

While the mode of action of nonsteroidal antiinflammatory agents is unknown, numerous laboratory procedures are available for demonstrating antiinflammatory activity in animal tests. The primary test procedure used to assay antiinflammatory activity in this study was the antiultraviolet erythema test in guinea pigs.[5] Phenylbutazone and most other clinically effective nonsteroidal antiinflammatory drugs are active in this test which was made quantitative by using phenylbutazone as a standard in each experiment. Addition assays of antiinflammatory activity were employed for certain compounds. These included the rat paw edema test using kaolin as irritant,[6] the cotton pellet test[7] in which the per cent inhibition of granuloma was estimated, and the Randall and Selitto test[8] which

(1) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol. Exptl. Therap.*, **138**, 405 (1962).

(2) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963).

(3) (a) T. Y. Shen, *et al.*, *J. Am. Chem. Soc.*, **85**, 488 (1963); (b) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exptl. Therap.*, **141**, 369 (1963).

(4) S. S. Adams, E. R. Cliffe, B. Lessel, and J. S. Nicholson, *Nature*, **200**, 271 (1963).

(5) C. V. Winder, J. Wax, V. Burr, M. Bean, and C. E. Rosiere, *Arch. Intern. Pharmacodyn.*, **116**, 261 (1958).

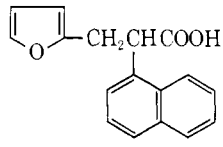
(6) D. Lorenz, *Arch. Exptl. Pathol. Pharmakol.*, **241**, 516 (1961).

(7) I. E. Bush and R. W. Alexander, *Acta Endocrinol.*, **35**, 268 (1960).

(8) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

measures mild analgesic and antipyretic activity in addition to antiinflammatory activity. Another method used to measure analgesic activity was the writhing test in mice, incorporating dye release.[9] Antipyretic activity was also estimated in rabbits using TAB vaccine as pyretic agent.[10]

Compounds relevant to this study are arylacetic acids, and the investigation originated with the observation that α-(1-naphthyl)-2-furanpropionic acid (I) had activity in the ultraviolet erythema test.



I

Activity relative to phenylbutazone was 0.25 and numerous related structures were synthesized for the purpose of studying structure–activity relationships.

Structure–Activity Relationships.—Recorded in Table I are the activities of the compounds in the ultraviolet erythema test. One of the most notable features is that the activity is clearly associated with the 1-naphthaleneacetic acid moiety (XXXVIII) and that this activity is retained or enhanced by the introduction of a double bond or aromatic system linked to the α-carbon atom by a methylene group. In addition to the 2-furyl group (I), other π-electron systems which show this effect are 2-thienyl (II), 2-, 3-, and 4-pyridyl (III, IV, and V, respectively), and phenyl (VI). Saturated alkyl groups on the α-carbon atom of 1-naphthaleneacetic acid cause a loss of antiultraviolet erythema activity. The enhancement of antiultraviolet erythema activity by the 2-furfuryl group on the α-carbon atom of 1-naphthaleneacetic acid is parallelled in the case of phenylacetic acid. While the latter compound XL is inactive, the furfuryl derivative XXI has activity in the antiultraviolet erythema test. Another point of some interest is the activity of arylacetic acids containing various aryloxy groups on the α-carbon atom, in particular the β-(2,6-xylyloxy)ethyl derivative of 1-naphthaleneacetic acid (XIV). The activity of the thianaphtheneacetic acids XLVI and XLVII is also of interest in relation to the naphthaleneacetic acid series.

Under the same conditions, 4-isobutylphenylacetic acid (ibufenac) had activity 0.13 times phenylbutazone in the test procedure, and 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (indomethacin) had 1.3 times the activity of phenylbutazone. Also included in Table I are the activities found for aspirin, mefenamic acid, and flufenamic acid. The antiultraviolet erythema activity of the 1-naphthaleneacetic acid derivatives, such as I and the thianaphtheneacetic acids, appears of a similar order to the phenylacetic acid derivative ibufenac and is also comparable with aspirin and mefenamic acid. The order of antiultraviolet erythema activity is lower than the 3-indoleacetic acid derivative indomethacin, and also lower than flufenamic acid and phenylbutazone.

Further Pharmacology.—Activity of compounds in this study in rat paw edema tests was dependent on the irritant used. Although activity comparable to phenylbutazone was exhibited by certain compounds, particularly I, II, III, and IV in formalin- and egg albumin induced edema tests,[11] activity in similar tests using yeast or kaolin as irritant was, in general, only slight. In the latter test, I had activity 0.05 phenylbutazone and IV, VI, XII, XIV, XXI, and XLVI were inactive at 200 mg./kg. A notable exception was the N-piperidinylethyl derivative XX which has activity 0.25 times phenylbutazone in this test. Of possible relevance to this latter observation is the reported activity of α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthaleneacetamide against edema induced by kaolin, dextran, serotonin, formalin, and carrageenin.[12] In comparison, aspirin, mefenamic acid, flufenamic acid, and ibufenac had activity 0.4, 0.5, 0.8, and 0.25 times phenylbutazone, respectively, against kaolin-induced edema. In a test for inhibition of granuloma formation by the insertion of cotton pellets in the axillae of rats, I had significant activity at 200 mg./kg./day *p.o.*, while phenylbutazone was active at 75 mg./kg./day *p.o.* In the method of Randall and Selitto, I, IV, VI, XII, XXI, XXXVIII, and XLVI were inactive in the antiinflammatory (yeast irritant), antipyretic, and analgesic parameters at 200 mg./kg. Compounds XIX and XX were active in the analgesic and antipyretic parameters but inactive in the antiinflammatory parameter at 200 mg./kg. Phenylbutazone and indomethacin showed the same activity as the latter compounds in this test at 50 mg./kg. and 20 mg./kg., respectively. Aspirin was only active in this test at a dose of 300 mg./kg. (all parameters). In the writhing test, the only compound in the series which showed significant analgesic activity was XX (1.4 times phenylbutazone). In antipyretic studies in rabbits, none of the compounds in the series which was examined showed significant activity. By comparison, phenylbutazone was active at 75 mg./kg., aspirin was active at 250 mg./kg., and mefenamic acid was slightly active at 100 mg./kg. Flufenamic acid and ibufenac were inactive at 200 mg./kg. From the preceding data, it appears that, unlike the clinically effective drugs, none of the compounds in this series of arylacetic acids have antiinflammatory activity combined with significant analgesic and antipyretic activity. The order of antiinflammatory activity for the more active compounds in the series appears comparable to ibufenac and also aspirin and mefenamic acid.

Compound I is a powerful uncoupler of oxidative phosphorylation in rat liver mitochondria.[13] It has been claimed that this latter property parallels antiinflammatory potency and each of the drugs, phenylbutazone, salicylic acid, mefenamic acid, flufenamic acid, and indomethacin, shows this effect.[14] The approximate concentration of I for 50% inhibition of hepatic oxidative phosphorylation was 0.25 m*M*, while the concentrations of ibufenac, salicylic acid, and

(9) B. A. Whittle, Communication to the British Pharmacological Society Meeting, July 1963.

(10) J. A. Baker, J. Hayden, P. G. Marshall, C. H. R. Palmer, and T. D. Whittet, *J. Pharm. Pharmacol.*, **15**, 97T (1963).

(11) Personal communication from Mr. L. Fontaine, Laboratoire Lipha.

(12) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964).

(13) Personal communication from Dr. M. W. Whitehouse.

(14) (a) M. W. Whitehouse and J. M. Haslam, *Nature*, **196**, 1323 (1962); (b) M. W. Whitehouse, *ibid.*, **201**, 629 (1964).

Table I

Antiultraviolet Erythema Activity of Arylacetic Acids and Derivatives

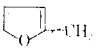
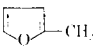
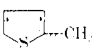
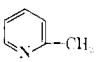
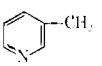
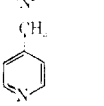
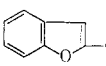
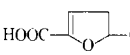
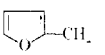
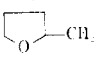
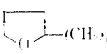
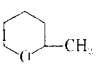
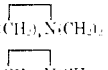
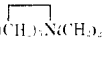
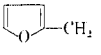
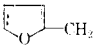
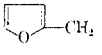
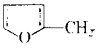
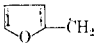
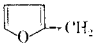
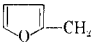
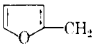
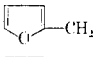
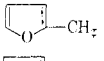
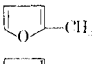
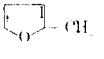
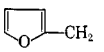
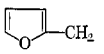
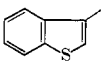
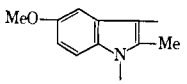
Compd.	Ar	R	X	Antiultraviolet erythema activity	LD_{50}, mg./kg. p.o. (mice)
Phenylbutazone (standard)				1.0	
I	1-$C_{10}H_7$		ONa[a]	0.25	750
Ia	1-$C_{10}H_7$		ONa[a,b]	0.10	750
II	1-$C_{10}H_7$		ONa[a]	0.20	900
III	1-$C_{10}H_7$		OK[c]	0.25	125[d]
IV	1-$C_{10}H_7$		OK[c]	0.25	>2000
V	1-$C_{10}H_7$		OK[c]	0.14	>2000
VI	1-$C_{10}H_7$	$C_6H_5CH_2$	OH	0.16	>500
VII	1-$C_{10}H_7$	2-$CH_3OC_6H_4CH_2$	OH	0[e]	>2000
VIII	1-$C_{10}H_7$	2-$HOC_6H_4CH_2$	OH[f]	0[e]	>2000
IX	1-$C_{10}H_7$		OH	0[g]	>500
X	1-$C_{10}H_7$		OH	0.05	>1000
XI	1-$C_{10}H_7$	CH_2=$CHCH_2$	ONa[a]	0.12	>500
XII	1-$C_{10}H_7$	CH_3CH=$CHCH_2$	ONa[a]	0.10	750
XIII	1-$C_{10}H_7CH_2$		ONa[a]	0[e]	>500
XIV	1-$C_{10}H_7$	2,6-$(CH_3)_2C_6H_3O(CH_2)_2$	OH	0.17	>2000
XV	1-$C_{10}H_7$	CH_3	OH	0	>1000
XVI	1-$C_{10}H_7$		ONa[a]	0[g]	>500
XVII	1-$C_{10}H_7$		ONa[a]	0[e]	>500
XVIII	1-$C_{10}H_7$		ONa[a]	0[h]	500
XIX	1-$C_{10}H_7$		OK[c]	0[g]	1500
XX	1-$C_{10}H_7$		OK[c]	0[e]	2000
XXI	C_6H_5		OH	0.11	>500
XXII	2-$CH_3C_6H_4$		OH	0[d]	>500
XXIII	2-$CH_3OC_6H_4$		OH	0.06	>1000
XXIV	3,4-$(CH_3O)_2C_6H_4$		OH	0.07	>1000
XXV	4-ClC_6H_4		OH	0[g]	2000
XXVI	2-HOC_6H_4		OH[f]	0[e]	>500
XXVII	4-$(CH_3)_2CHCH_2C_6H_4$		OH	0[g]	>500
XXVIII	2-CH_3-1-$C_{10}H_6$		OH	0[e]	2000
XXIX	2-$C_{10}H_7$		OH	0.05	>500
XXX	9-$C_{14}H_9$[i]		OH	0[e]	>500
XXXI	1-$C_{10}H_7$		NH_2	0[e]	750
XXXII	1-$C_{10}H_7$		OCH_3	0[e]	>500

TABLE I (*Continued*)

Compd.	Ar	R	X	Antiultraviolet erythema activity	LD_{50}, mg./kg. *p.o.* (mice)
XXXIII	1-$C_{10}H_7$		$O(CH_2)_2NEt_2$	0.06	2000
XXXIV	1-$C_{10}H_7$		$NHNHCH(CH_3)_2$	0.03	>2000
XXXV	1-$C_{10}H_7$	CH_2=$CHCH_2$	$O(CH_2)_2NEt_2$	0.10	1000
XXXVI	1-$C_{10}H_7$	CH_3CH=$CHCH_2$	$O(CH_2)_2NEt_2$	0.05	>500
XXXVII	1-$C_{10}H_7$	CH_2=$CHCH_2$	$NHNHCH(CH_3)_2$	0.11	750
XXXVIII	1-$C_{10}H_7$	H	OH	0.12	>1000
XXXIX	2-CH_3-1-$C_{10}H_6$	H	OH	0[e]	>500
XL	C_6H_5	H	OH	0[e]	>500
XLI	C_6H_5	$C_6H_5CH_2$	OH	0.05	>500
XLII	C_6H_5	C_6H_5NH	OH	0[e]	>2000
XLIII	C_6H_5	2,3-$(CH_3)_2C_6H_3NH$	OH	0[e]	1000
XLIV	C_6H_5	C_6H_5O	OH	0.04	1000
XLV	C_6H_5	4-$C_2H_5CH(CH_3)C_6H_4O$	OH	0.12	>500
XLVI		H	OH	0.20	>2000
XLVII		H	OH	0.08	1500
	4-$(CH_3)_2CHCH_2C_6H_4$	H	OH	0.13	>1000
	 4-Cl-C_6H_4CO	H	OH	1.3	
4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione[i]				1.0	1000
Acetylsalicylic acid[k]				0.12	>2000
N,2,3-Xylylanthranilic acid[l]				0.12	2000
N-(α,α,α-Trifluoro-*m*-tolyl)anthranilic acid[m]				0.8	2000

[a] Sodium salt. [b] *l*-(−) isomer [c] K salt. [d] This compound exhibited hepatotoxicity in dogs. [e] Inactive at 200 mg./kg. *p.o.* [f] Lactone. [g] Slight activity at 200 mg./kg. *p.o.* [h] Inactive at 125 mg./kg. *p.o.* [i] 9-Phenanthryl. [j] Phenylbutazone. [k] Aspirin. [l] Mefenamic acid. [m] Flufenamic acid.

phenylbutazone were 1.5, 0.08, and 0.08–0.2 m*M*, respectively.

Synthetic Methods.—The α-substituted arylacetic acid derivatives listed in Table II were, in general, synthesized from the anions of arylacetonitriles by reaction with an alkyl halide followed by hydrolysis of the substituted arylacetonitrile. The anions were prepared using sodium hydride as a base and, preferentially, dimethylformamide as solvent. Hydrolysis of the nitriles was best accomplished by the use of benzyl alcoholic potassium hydroxide.[15] An alternative route used in certain cases was the Perkin condensation of the sodium salts of arylacetic acids with the required aldehyde, followed by reduction of the resultant acrylic acids with sodium amalgam.[16]

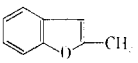
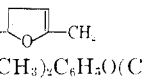
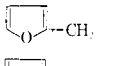
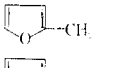
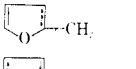
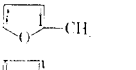
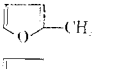
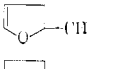
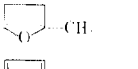
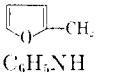
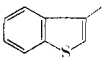
Experimental[17]

The preparation of compounds I, Ia, II–V, XI–XIII, XVI–XX, XXVIII, and XXX–XXXVII has been the subject of previous publications.[18] Compounds XXXVIII, XXXIX, XLI, and XLVI were obtained from commercial sources. Synthetic methods A and B, which were used for most of the remaining compounds, listed in Table II, employed commercially available halides and nitriles where possible. 2-Chloromethylfuran,[19] 2-methoxybenzyl chloride,[20] 2-chloromethylbenzofuran,[21] 2-(2,6-xylyloxy)ethyl bromide,[22] and 4-isobutylbenzyl cyanide[23] were made by procedures based on literature preparations. Listed in Table III are the physical data on the crystalline nitrile intermediates obtained. Liquid nitriles were purified by fractionation and characterized by infrared spectra and gas–liquid chromatography. Methods A and B are illustrated by the following examples.

α-(2-Methyl-1-naphthyl)-2-furanopropionic Acid (XXXIII). Method A.—A solution of 2-methyl-1-naphthaleneacetonitrile (19.8 g., 0.11 mole) in anhydrous dimethylformamide (300 ml.) was stirred under nitrogen during the addition of sodium hydride (4.91 g., 0.11 mole, of a 54% dispersion in mineral oil). The temperature was maintained below 40° with the aid of a cold-water bath. After addition, the reaction mixture was kept at 40° for 1 hr. to ensure completion of anion (orange-red color) formation and then cooled during the addition of 2-chloromethylfuran (13.4 g., 0.12 mole) in anhydrous benzene. The mixture was maintained at 30–40° for 2.5 hr., set aside at room temperature for 16 hr., and then carefully added to cold water and acidified with HCl. Extraction with ether followed by drying of the ether extracts (K_2CO_3) and concentration yielded crystalline α-(2-methyl-1-naphthyl)-2-furanpropionitrile, which was further purified by recrystallization from benzene–petroleum ether (b.p. 60–80°). The yield of nitrile, m.p. 114–117°, was 24.6 g. (86%). The nitrile (10.0 g., 0.038 mole) was hydrolyzed in benzyl alcoholic KOH (4%, 180 ml.) at reflux temperature for 16 hr. Concentration followed by solution of the residue in water, filtration, and acidification with 5 *N* HCl yielded the crude acid.

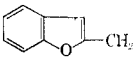
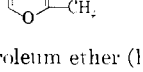
(15) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).
(16) D. Papa, U. S. Patent 2,606,922 (1952).
(17) Melting points were recorded using an Electrothermal apparatus comprising a gas-heated block and a thermometer calibrated for stem exposure. Infrared spectra were measured with a Hilger H800 instrument.
(18) (a) E. Szarvasi and L. Neuvy, *Bull. soc. chim. France*, 1343 (1962); (b) E. Szarvasi, *Compt. rend.*, **259**, 166 (1964); (c) E. Szarvasi and L. Fontaine, *Bull. soc. chim. France*, 3113 (1964).
(19) R. Lukeš and V. Dienstbierová, *Chem. Listy*, **48**, 280 (1954).
(20) M. Simonetta and G. Favini, *J. Chem. Soc.*, 1840 (1954).
(21) R. R. Gaertner, *J. Am. Chem. Soc.*, **73**, 4400 (1951).
(22) P. Hey and G. L. Willey, *Brit. J. Pharmacol.*, **9**, 471 (1954).
(23) Boots Pure Drug Co., Belgium Patent 621,255 (1962).

TABLE II
ARYLACETIC ACIDS
$ArCH(R)COOH$

Compd.	Ar	R	M.p., °C.[a]	Overall yield,[b] %	Method[c]	Formula	%C Calcd.	%C Found	%H Calcd.	%H Found
VI	1-$C_{10}H_7$	$C_6H_5CH_2$	90.5–93[d]	16	B	$C_{19}H_{16}O_2$	82.58	82.71	5.84	6.03
VII	1-$C_{10}H_7$	2-$CH_3OC_6H_4CH_2$	148–150	37	A	$C_{20}H_{18}O_3$	78.41	78.70	5.92	5.84
VIII	1-$C_{10}H_7$	2-$HOC_6H_4CH_2$[e]	165.5–168	90[f]	..	$C_{18}H_{14}O_2$	83.20	82.93	5.15	5.11
IX	1-$C_{10}H_7$		186–187[g]	42	A	$C_{21}H_{16}O_3$	79.73	79.93	5.10	5.38
X	1-$C_{10}H_7$		190–193[h]	37	B	$C_{18}H_{14}O_5$[i]	69.68	68.80	4.55	4.73
XIV	1-$C_{10}H_7$	2,6-$(CH_3)_2C_6H_3O(CH_2)_2$	100–100.5	9	A	$C_{22}H_{22}O_3$	79.04	79.32	6.63	6.50
XV	1-$C_{10}H_7$	CH_3	148.5–152[j,k]	60	A	$C_{13}H_{12}O_2$	78.00	78.13	6.05	6.17
XXI	C_6H_5		105–106[k]	26	B	$C_{13}H_{12}O_2$	72.33	72.00	5.60	5.46
XXII	2-$CH_3C_6H_4$		49.5–51[l]	40	A	$C_{14}H_{14}O_3$	73.02	73.06	6.13	6.21
XXIII	2-$CH_3OC_6H_4$		81–82	7	C	$C_{14}H_{14}O_4$	68.28	68.64	5.73	5.68
XXIV	3,4-$(CH_3O)_2C_6H_3$		101–102	11	C	$C_{15}H_{16}O_5$	65.21	65.04	5.85	5.97
XXV	4-ClC_6H_4		100–103	19	B	$C_{13}H_{11}ClO_3$[m]	62.28	62.12	4.42	4.47
XXVI	2-HOC_6H_4[e]		60–62	19	C	$C_{13}H_{12}O_4$	72.89	72.92	4.70	4.84
XXVII	4-$(CH_3)_2CHCH_2C_6H_3$		93–94.5	7	A	$C_{21}H_{26}O_3$	74.97	75.20	7.40	7.53
XXVIII	2-CH_3-1-$C_{10}H_6$		144–148	73	A	$C_{14}H_{16}O_3$	77.12	76.87	5.75	5.93
XXIX	2-$C_{10}H_7$		115–116	14	C	$C_{17}H_{14}O_3$	76.67	76.86	5.30	5.40
XXX	9-$C_{14}H_9$[n]		144–148.5	17	C	$C_{21}H_{16}O_3$	79.73	79.40	5.10	5.02
XLII	C_6H_5	C_6H_5NH	173.5–175.5[o]	65	..	$C_{14}H_{13}NO_2$	73.99	74.19	5.77	5.88
XLIII	CH_3	2,3-$(CH_3)_2C_6H_3NH$	127–129	67	..	$C_{16}H_{17}NO_2$[p]	75.27	74.93	6.71	6.70
XLIV	C_6H_5	C_6H_5O	107–111[q]	41	..	$C_{14}H_{12}O_3$	73.67	73.86	5.30	5.36
XLV	C_6H_5	4-$C_2H_5CH(CH_3)C_6H_3O$	101–103	7	..	$C_{18}H_{20}O_3$	76.03	76.09	7.09	7.24
XLVI		H	111–112.5[r]	42	..	$C_6H_6O_2S$	62.48	62.13	4.19	3.99

[a] Recrystallizations from petroleum ether or benzene–petroleum ether unless otherwise indicated. [b] Based on conversion from $ArCH_2CN$, $ArCH_2COONa$, or $ArCH(Br)COOEt$. [c] See Experimental. [d] Lit.[15] m.p. 93–95°. [e] Lactone. [f] From VII. [g] From aqueous EtOH. [h] From $CHCl_3$–petroleum ether [i] *Anal.* Calcd.: equiv. wt., 155. Found: equiv. wt., 157. [j] F. F. Blicke and R. F. Feldkamp [*J. Am. Chem. Soc.*, **66**, 1087 (1944)] quote m.p. 148–149°. [k] Lit.[16] m.p. 105°. [l] B.p. 150° (0.5 mm.). [m] *Anal.* Calcd.: Cl, 14.15. Found: Cl, 14.05. [n] 9-Phenanthryl. [o] F. Tiemann and K. Piest [*Chem. Ber.*, **15**, 2030 (1882)] quote m.p. 173–175°. [p] *Anal.* Calcd.: N, 14.15. Found: N, 14.05. [q] R. Meyer and H. Boner [*Ann.*, **220**, 51 (1883)] quote m.p. 108°. [r] Lit.[25] m.p. 108–109°.

TABLE III
NITRILES
$ArCH(R)CN$

Ar	R	Recrystn. solvent[a]	M.p., °C.	Formula	%C Calcd.	%C Found	%H Calcd.	%H Found
1-$C_{10}H_7$	$C_6H_5CH_2$	E	75–77[b]	$C_{19}H_{15}N$[c]	88.68	88.66	5.88	5.64
1-$C_{10}H_7$	2-$CH_3OC_6H_4CH_2$	PE	110–113	$C_{20}H_{17}NO$[d]	83.59	83.64	5.96	5.73
1-$C_{10}H_7$		B–PE	103–105	$C_{21}H_{15}NO$	84.92	84.90	5.20	5.09
1-$C_{10}H_7$	2,6-$(CH_3)_2C_6H_3O(CH_2)_2$	PE	63–69	$C_{22}H_{21}NO$[e]	83.77	84.04	6.71	6.83
2-CH_3-1-$C_{10}H_6$		PE	116–118	$C_{18}H_{15}NO$	83.05	82.99	5.81	5.93

[a] E, ethanol; PE, petroleum ether (b.p. 60–80°); B, benzene. [b] Bun-Hoï and P. Cagniant [*Rec. trav. chim.*, **64**, 355 (1954)] quote 75°. [c] *Anal.* Calcd.: N, 5.44. Found: N, 5.34. [d] *Anal.* Calcd.: N, 4.88. Found: N, 5.00. [e] *Anal.* Calcd.: N, 4.44. Found: N, 4.27.

Recrystallization from benzene-petroleum ether afforded 8.6 g. (85%) of the acid, m.p. 143–147°.

α-(4-Chlorophenyl)-2-furanopropionic Acid (XXV). Method B.—4-Chlorobenzyl cyanide (25.5 g., 0.17 mole) was dissolved in dry benzene and treated with sodium hydride (7.4 g., 0.17 mole, of 54% dispersion in mineral oil) under anhydrous conditions in a nitrogen atmosphere. After addition, the mixture was heated under reflux for 3 hr. by which time formation of the anion (yellow) appeared complete. A solution of 2-chloromethylfuran (19.6 g., 0.17 mole) in anhydrous benzene was added, with stirring and after addition the mixture was heated under reflux for 3 hr., cooled, filtered, and fractionated. The fraction [10.8 g., b.p. 126–128° (0.1 mm.), $n^{22}D$ 1.5518] contained at least 96% of the required nitrile as indicated by infrared spectra and gas–liquid chromatography. Hydrolysis with benzyl alcoholic KOH in the manner described in the previous example yielded 7.9 g. of the crude acid, m.p. 84–96°. Recrystallization from petroleum ether yielded 6.1 g. of the pure product, m.p. 100–104°.

Synthesis *via* Acrylic Acids. Method C.—This method was only of proven advantage in the case of XXX. All attempts to synthesize this compound from 9-phenanthreneacetonitrile and 2-chloromethylfuran were unsuccessful.

α-(9-Phenanthryl)-2-furanpropionic Acid (XXX). Method C.—A mixture of sodium 9-phenanthreneacetate[24] (6.4 g., 0.03 mole), 2-furaldehyde (2.38 g., 0.03 mole), and acetic anhydride (12 g.) was heated under reflux for 3 hr. and then heated at 110–120° for 3 hr. The mixture was cooled, added to water, and stirred vigorously. The oily solid which precipitated was separated, suspended in water, and acidified with HCl. The crude acid obtained was dissolved in benzene, filtered, and diluted with petroleum ether affording the acrylic acid (2.3 g.), m.p. 237–240°. This product (1.87 g.) was dissolved in ethanol, and the solution was stirred vigorously during the gradual addition of 5% sodium amalgam (12 g.). After decantation from mercury residues, the solution was filtered and concentrated. The residual solid was dissolved in water and carefully acidified with 5 *N* HCl (pH 6). The precipitated acid was separated and recrystallized from benzene–petroleum ether. The yield was 1.03 g., m.p. 144–148.5°.

α-(2-Hydroxyphenyl)-2-furanacrylic Acid.—Sodium *o*-hydroxyphenylacetate (45.7 g., 0.26 mole) was treated with 2-furaldehyde (25.8 g., 0.26 mole) and acetic anhydride (108 g.) at reflux temperature for 6 hr. The product was isolated in the manner described in the previous experiment and recrystallized from ether–petroleum ether affording the acrylic acid (30.0 g., 50%), m.p. 151.5–152.5°; infrared (Nujol), strong band at 1680 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 68.08; H, 4.43.

Heating a sample (0.1 g.) of the acrylic acid at 180° for 5 min. yielded the **γ-lactone** (0.07 g., 76%), m.p. 108–111° (from aqueous ethanol); infrared (KBr), strong band at 1771 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.63; H, 4.05.

α-(2-Hydroxyphenyl)-2-furanpropionic Acid γ-Lactone (XXVI).—Reduction of the foregoing acrylic acid (10.0 g., 0.0843 mole) with 86 g. of 5% NaHg in ethanol yielded an oil. Distillation afforded the crystalline lactone (3.5 g., 38%), b.p. 136–138° (0.1 mm.), m.p. 60–62° (from petroleum ether); infrared (KBr), strong band at 1804 cm.$^{-1}$ (C=O).

3-(1-Naphthyl)hydrocoumarin (VIII).—α-(1-Naphthyl)-2-methoxyphenylpropionic acid (VII, 1.0 g., 3.3 mmoles) was dissolved in a mixture of 50% HBr (4 ml.) and glacial acetic acid (3 ml.). The mixture was heated under reflux, with stirring, for 3 hr. and then cooled. The solid which had precipitated from the solution was separated, washed with water, and dried affording the dihydrocoumarin (0.81 g., 90%), m.p. 167.5–170°, unchanged on recrystallization from ethanol; infrared (KBr), strong band at 1752 cm.$^{-1}$ (C=O).

(24) E. Mosettig and J. Van de Kamp, *J. Am. Chem. Soc.*, **55**, 2999 (1933).

Preparation of N,2-Diphenylglycine and Derivatives.—Ethyl α-bromo-α-phenylacetate was obtained from ethyl phenylacetate and N-bromosuccinimide by the procedure of Boyer and Straw,[25] but it was found necessary to add a catalytic quantity of benzoyl peroxide to obtain a satisfactory yield (88%). Reaction with aniline in benzene yielded N,2-diphenylglycine ethyl ester,[26] m.p. 87.5–89.5°, in 81% yield. Saponification with aqueous ethanolic NaOH followed by careful neutralization with 5 *N* HCl afforded N,2-diphenylglycine (XLII), m.p. 173.5–175.5° (from benzene), in 65% yield. In a similar way, reaction of ethyl α-bromo-α-phenylacetate with 2,3-xylidine yielded 2-phenyl-N-(2,3-xylyl)glycine ethyl ester, m.p. 55–56° (from petroleum ether), in 45% yield.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.23; H, 7.59; N, 4.88.

Saponification yielded 2-phenyl-N-(2,3-xylyl)glycine (XLIII), m.p. 127–129° (from benzene–petroleum ether), in 67% yield.

α-Phenoxyphenylacetic Acid (XLIV).—A mixture of phenol (4.7 g., 0.05 mole), ethyl α-bromo-α-phenylacetate (12.1 g., 0.05 mole), K_2CO_3 (6.9 g.), and acetone (50 ml.) was heated under reflux, with stirring, for 4 hr. After filtration and concentration, the residual ester was saponified directly with 2.5 *N* NaOH (40 ml.) at reflux temperature for 45 min., and cooling and acidification with 5 *N* HCl precipitated the acid which was separated and recrystallized from benzene–petroleum ether, yielding 4.7 g. (41%), m.p. 107–111°.

α-(4-*sec*-Butylphenoxy)phenylacetic Acid (XLV).—4-*sec*-Butylphenol (27.63 g., 0.11 mole) was treated with ethyl α-bromo-α-phenylacetate (16.95 g., 0.11 mole), K_2CO_3 (15.6 g.), and acetone (100 ml.) in the manner described in the previous experiment. The acidic product obtained was an oil which crystallized after drying ($CaCl_2$) *in vacuo* followed by trituration with cold petroleum ether. Recrystallization from benzene–petroleum ether yielded 6.2 g. of the acid, m.p. 89–92°. Further recrystallization from benzene–petroleum ether gave a first crop of slightly impure material (0.9 g.), m.p. 101–103° (with shrinking), followed by the pure acid (2.0 g.), m.p. 103.5–105°.

3-Thianaphtheneacetic Acid (XLVI).—Chloromethylation of thianaphthene, followed by cyanide displacement and hydrolysis yielded the acid in 47% yield (over-all). The procedure of Blicke and Sheets[27] was improved by using dimethyl sulfoxide as solvent for the cyanide displacement.

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(25) J. H. Boyer and D. Straw, *ibid.*, **75**, 1642 (1953).
(26) M. Julia and G. Tchernoff, *Bull. soc. chim. France*, 661 (1958).
(27) F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).