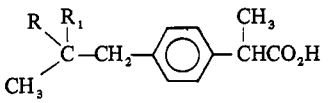
# Synthesis and Antiinflammatory Activities of (α-Cyclopropyl-*p*-tolyl)acetic Acid and Related Compounds

G. Rovnyak,* P. A. Diassi, S. D. Levine, and J. T. Sheehan

*The Squibb Institute for Medical Research, Princeton, New Jersey 08540.* *Received June 8, 1972*

The synthesis and antiinflammatory activities of (α-cyclopropyl-*p*-tolyl)acetic acid (**1**) and related compounds are presented. The nature of the products formed during cyanide displacement reactions on α-bromo-*p*-tolyl cyclopropyl ketone (**6**) and *p*-(1-bromoethyl)phenyl cyclopropyl ketone (**10**) under a variety of conditions is described.

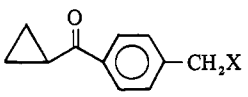
The chemical and theoretical interest in small-ring compounds has been extended to biological systems by Burger and coworkers,[1] who suggest that the high electron density of the three-membered ring may possibly provide a focus for enzyme attachment. Moreover, the principal urinary metabolites[2a] of the known antiinflammatory agent, 2-[*p*-(isobutylphenyl)]propionic acid (**2**),[2] are the hydroxy acid **3** and the diacid **4**. A compound in which the isobutyl group is replaced by the sterically similar, but electronically dissimilar, cyclopropylmethyl moiety (*e.g.*, **1**) might be expected to suffer an altered metabolic fate, which could be reflected in its biological profile.



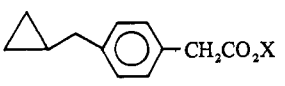
**2**, R = $CH_3$; $R_1$ = H
**3**, R = $CH_3$; $R_1$ = OH
**4**, R = $CO_2H$; $R_1$ = H

Our initial approach to these compounds involved the Friedel–Crafts acylation of ethyl phenylacetate[3] with either cyclopropylcarbonyl chloride or γ-chlorobutyryl chloride.[4] However, these reactions failed under a variety of conditions, and unreacted ester was recovered.

The synthesis of **1** was begun with acylation of toluene with cyclopropylcarbonyl chloride to give, almost exclusively, the para isomer **5**.[4a] Benzylic monobromination of **5** with *N*-bromosuccinimide in refluxing $CCl_4$, followed by cyanation with NaCN in DMF, gave the nitrile **7**. Alkaline hydrolysis of **7** afforded the penultimate compound **8**, which was reduced under modified Wolff–Kishner conditions to give **1**.

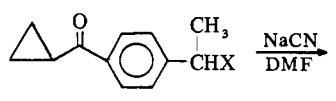


**5**, X = H
**6**, X = Br
**7**, X = CN
**8**, X = $CO_2H$
**21**, X = $CO_2Na$

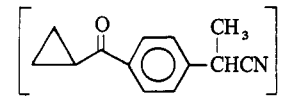


**1**, X = H
**22**, X = Na

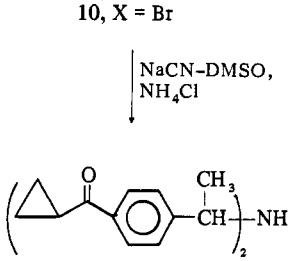
Having what appeared to be a general procedure, we applied this reaction sequence to the next higher homolog. In this way, using ethylbenzene in the acylation step, intermediates **9** and **10** were prepared. Cyanation of **10** with NaCN in DMF gave, without isolation of **11**, the desired acid **12** in low (*ca.* 10%) yield after hydrolysis. The major reaction product (40%) was the bis compound **13**, produced by base-catalyzed alkylation of the initially formed nitrile **11** with a second molecule of **10**. The yield of **12** was not improved by variation of the conditions. The inclusion of $NH_4Cl$ in the reaction medium, in an attempt to suppress the formation of **13**, gave the secondary amine **14** as the major product. The support for structure **14**, which has not been rigorously proved, is derived from its nmr and ir spectra (see Experimental Section) and by analogy with the major product (55%) formed when the primary bromide **6** was allowed to react under similar conditions. This latter product has been identified as tris[*p*-(cyclopropylcarbonyl)benzyl]amine (**15**). The nmr spectrum is consistent with the assigned structure but is not definitive, since it is nearly superimposable with that of the desired nitrile **7**. The major difference is an upfield shift (12 cps relative to **7**) of the singlet assigned to the benzylic protons of **15**. The mass ($M^+$ = 491) and ir [1657 $cm^{-1}$ (C=O) and lack of C≡N and NH absorptions] spectra and microanalytical data confirm the assigned structure. The tertiary amine is formed probably because reaction occurs at a primary center rather than at the more sterically hindered secondary center as in the previous example.



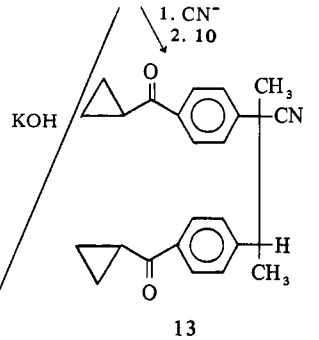
**9**, X = H
**10**, X = Br



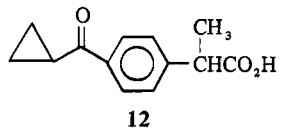
**11**



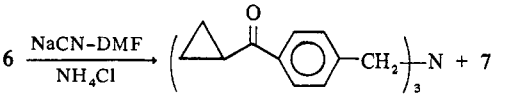
**14**



**13**



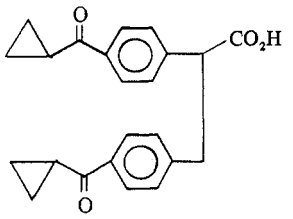
**12**



**15** (as HCl salt)

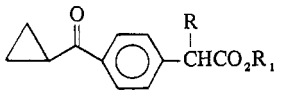
The isolation of the bis compound **13** in the homologous sequence prompted us to seek the corresponding bis compound in the parent reaction. Hydrolysis of crude nitrile **7** afforded, after isolation of **8**, a small amount of an acid having the expected structure **16**.

Having been unsuccessful in applying the general scheme to the higher homolog on a practical synthetic scale, we used an alternate approach, employing monomethylation[5] of ester **17**. In this way, the keto acid **8** was esterified and alky-

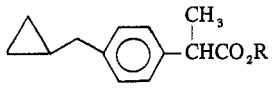


16

lated to give the propionate ester **18**, which was hydrolyzed to the keto acid **12**† and reduced to the oily acid **19**. The corresponding sodium salts of **19**, **8**, and **1** (**20**, **21**, and **22**, respectively) were also prepared for comparison of their biological activities.

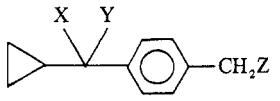


**8**, R = $R_1$ = H
**17**, R = H; $R_1$ = $CH_3$
**18**, R = $R_1$ = $CH_3$
**12**, R = $CH_3$; $R_1$ = H



**19**, R = H
**20**, R = Na·2$H_2O$

Seven additional derivatives **23–26** and **28–30**, that retained the basic carbon skeleton, were prepared by standard methods (see Experimental Section) as representatives of other functional classes.



| | X | Y | Z |
|---|---|---|---|
| 23 | H, | H | $CH_2OH$ |
| 24 | H, | OH | $CH_2OH$ |
| 25 | H, | OH | $CO_2H$ |
| 26 | O | | CONHOH |
| 27 | O | | COCl |
| 28 | O | | $CONH_2$ |
| 29 | O | | $CO_2$-*i*-$C_3H_7$ |
| 30 | O | | $CO_2CH_2CH_2N(CH_3)_2$·HCl |

**Antiinflammatory Activity.**‡ The test compounds were administered orally as a suspension in 1% CMC to fasted (16–18 hr), 180–200-g, young-adult male Sprague–Dawley rats (seven per dose group) that were allowed $H_2O$ *ad libitum*. Two hours later, the volume of the left hind paw was measured by Hg displacement, and 0.05 ml of a 1% solution of carrageenin in sterile pyrogen-free 0.9% NaCl solution was injected into the paw. Three hours later, the volume of the paw was again measured by Hg displacement.

Table I lists the antiinflammatory activities found for the compounds of interest, along with the activities of two standard compounds, ibufenac and sodium phenylbutazone. Of interest are the essentially equivalent activities observed for the cyclopropylcarbonyl derivatives **8** and **21** and for the cyclopropylmethyl derivatives **1** and **22**, respectively. At an intermediate level of oxidation, the cyclopropylhydroxymethyl derivative **25** was found to be devoid of activity. α-Alkylation gave derivatives of similar (**19** and **20** vs. **1** and **22**, respectively) or lesser (**12** and **16** *vs.* **8**) activity. On the other hand, carboxyl modification (**23**, **24**, **26**, and **28–30**) gave compounds that were, as a group, less active than the corresponding free acid.

Table I

| Compd | $ID_{50}$,[a] mg/kg | Compd | $ID_{50}$,[a] mg/kg |
|---|---|---|---|
| 1 | 85 | 23 | 95 |
| 8 | 63 | 24 | Inactive |
| 12 | >150 | 25 | Inactive |
| 16 | >150 | 26 | >150 |
| 19 | 65 | 28 | 138 |
| 20 | 37 | 29 | 62 |
| 21 | >38, 18 | 30 | 102 |
| 22 | 40 | Ibufenac | 55 |
| | | Sodium phenylbutazone | 100 |

[a] Concentration inhibiting carageenin-induced edema by 50%.

On the basis of these results, compounds **1**, **8**, **21**, and **22** were evaluated further in a variety of antiinflammatory assays, and a detailed presentation and analysis of the biological activities of these compounds will be forthcoming from these laboratories.

## Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were determined using a Perkin-Elmer IR-621 spectrometer, and nmr spectra were determined on a Varian A-60 or Perkin-Elmer R-12B instrument in $CDCl_3$ (unless otherwise noted) with added TMS. Mass spectra were determined on a MS-902 spectrometer. Organic solutions were dried ($CaCl_2$) and all evaporations were carried out *in vacuo*. Silica gel (F-254 precoated tlc and plc plates and HF-254, Merck, AG) and alumina (neutral, Merck, AG) were used for chromatography and the compounds were detected by uv. Where analyses are indicated only by the symbols of the elements, analytical results for those elements were within 0.4% of the theoretical values.

**Cyclopropyl *p*-Tolyl Ketone (5).** To a cooled (ice bath) solution of cyclopropylcarbonyl chloride (104.5 g, 1 mol) in toluene (500 ml) was added anhydrous $AlCl_3$ (147 g, 1.1 mol) at such a rate that the temperature was maintained at 5–10° (addition time 1.5 hr). The mixture was poured onto ice (1 kg), and hexane (500 ml) was added. The organic fraction was separated, washed ($H_2O$), dried, and concentrated. The residual oil solidified on standing and was recrystallized (hexane) to give **5** (120 g, 75%), mp 48–50°. **5**, prepared by Close[4a] from γ-chlorobutyryl chloride and $PhCH_3$, followed by base-catalyzed ring closure, gave mp 49–51°.

**α-Bromo-*p*-tolyl Cyclopropyl Ketone (6).** A stirred solution of **5** (93 g, 0.58 mol) and NBS (98 g, 0.55 mol) in $CCl_4$ (500 ml) was heated slowly while being irradiated with long-wavelength uv light (Black-Ray, Model B-100A). After refluxing for 2 hr, the solution was cooled and the solids were collected and washed ($CCl_4$). The combined filtrates were washed (10% aqueous NaOH and $H_2O$), dried, and concentrated. The residual oil solidified and the crude product was crystallized (hexane) to give **6** (81 g, 52.5%), mp 69–71°. *Anal.* Calcd for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64; Br, 33.43. Found: C, 54.97; H, 4.71; Br, 34.45.

**[*p*-(Cyclopropylcarbonyl)phenyl]acetonitrile (7).** To a cooled (ice bath) stirred suspension of NaCN (17.2 g, 0.35 mol) in DMF (400 ml) was added a solution of **6** (76 g, 0.318 mol) in DMF (200 ml) at such a rate that the temperature was maintained at 10°. Stirring was continued for 2 hr and the temperature was allowed to increase to 20°. The resultant mixture was poured onto ice (800 g) and extracted ($Et_2O$). The extract was dried, treated with Darco, and concentrated. The residual oil was extracted with hot hexane (3 l.) which, upon cooling to 5°, gave **7** (30.4 g, 51.5%). Recrystallization (hexane) afforded the analytical sample, mp 84–86°. *Anal.* ($C_{12}H_{11}NO$) C, H, N.

**[*p*-(Cyclopropylcarbonyl)phenyl]acetic Acid (8), Sodium [*p*-(Cyclopropylcarbonyl)phenyl]acetate (21), and 2,3-Bis[*p*-(cyclopropylcarbonyl)phenyl]propionic Acid (16).** Crude compound **7** (9.45 g, 0.051 mol) was hydrolyzed in refluxing 15% aqueous ethanolic KOH. The mixture was concentrated and the residue was diluted ($H_2O$) and washed ($CHCl_3$). The aqueous layer was acidified (concentrated HCl) and extracted ($Et_2O$). The extract was dried, treated with Darco, and concentrated. The crude solid product was sublimed [115° (0.04 mm)] and recrystallized (EtOAc–hexane) to give **8** (7.0 g, 67%). *Anal.* ($C_{12}H_{12}O_3$) C, H.

†It was found that purification of **12** prepared in this way could be effected by recrystallization only if the major contaminant was dialkylated compound rather than unalkylated starting material **8**. Hence, reaction conditions were chosen that gave slight overalkylation.

‡The method used was a modification of ref 6.

A solution ($CHCl_3$) of **8** was shaken with aqueous NaOH (0.95 equiv). The aqueous layer was separated, washed ($CHCl_3$), concentrated, and dried under high vacuum at 100–130° to give the sodium salt **21**, mp 232–234°. *Anal.* ($C_{12}H_{11}O_3Na$) C, H, Na.

The sublimate residue afforded, upon preparative tlc (silica gel, 3:2 $CHCl_3$–EtOAc), 67 mg of the bis product **16**. Recrystallization (EtOAc–hexane) afforded the analytical sample: mp 159–160.5°; ir (KBr) 1645, 1660 (two C=O), 1730 $cm^{-1}$ ($CO_2H$); nmr δ 10.42 (s, 1 H, $CO_2H$), 7.92, 7.34 (2 d, 4 H, 2-ArH, $J$ = 8 Hz), 7.83, 7.14 (2 d, 4 H, 3-ArH, $J$ = 8 Hz), 3.96 (t, 1 H, $CHCO_2H$, $J$ = 7 Hz), and 3.39, 3.20 (2 d, 2 H, $CH_2CHCO_2H$, $J$ = 7 Hz); mass spectrum $M^+$ = 362. *Anal.* ($C_{23}H_{22}O_4$) C, H.

**(α-Cyclopropyl-p-tolyl)acetic Acid (1) and Sodium (α-Cyclopropyl-p-tolyl)acetate (22).** A solution of **8** (4 g, 0.019 mol) in 85% $N_2H_4$ (4.4 g) was refluxed for 1 hr and then cooled to 50°. KOH (4.4 g) was refluxed for 1 hr and then cooled to 50°. KOH (4.4 g) was added and the mixture was heated slowly to reflux. After $N_2$ evolution had ceased (*ca.* 2 hr), excess $N_2H_4$ was removed *in vacuo* and the residue was diluted ($H_2O$) and washed ($CHCl_3$). The aqueous layer was acidified (concentrated HCl) and extracted ($CHCl_3$). The extract was dried and concentrated to give a crude solid product that was recrystallized (hexane) to give **1** (3.35 g, 90%). *Anal.* ($C_{12}H_{14}O_2$) C, H.

The sodium salt of **1** was prepared as above to give **22**, mp 208.5–210°. *Anal.* ($C_{12}H_{13}O_2Na$) C, H, Na.

**Cyclopropyl p-Ethylphenyl Ketone (9).** **9** was prepared by the procedure described for **5**. Thus, from cyclopropylcarbonyl chloride (31.4 g, 0.3 mol) and ethylbenzene (250 ml), there was obtained **9** (41.5 g, 80%) as a clear liquid, bp 88–92° (0.5 mm). *Anal.* ($C_{12}H_{14}O$) C, H.

**p-(1-Bromoethyl)phenyl Cyclopropyl Ketone (10).** **10** was prepared by the procedure described for **6**. From **9** (19 g, 0.11 mol) there was obtained **10** (20.3 g, 76%), mp 53–54°. *Anal.* ($C_{12}H_{13}BrO$) C, H, Br.

**p-(Cyclopropylcarbonyl)hydratropic Acid (12) and 2,3-Bis[p-(cyclopropylcarbonyl)phenyl]-2-methylbutyronitrile (13). Method A.** To a slurry of NaCN (0.611 g, 12.5 mmol) in DMF (25 ml) was added, at ambient temperature, a solution of **10** (2.53 g, 10 mmol) in DMF (10 ml), and the reaction mixture was stirred for 24 hr. The solution was diluted with an equal volume of cold $H_2O$ and extracted ($Et_2O$). The extract was dried, treated with Darco, and concentrated to give an oil (1.69 g). Preparative tlc (silica gel, 3:2 EtOAc–hexane) of a portion (200 mg) of this oil afforded **13** (84 mg, 35%): mp 181.5–182°; ir (KBr) 2237 $cm^{-1}$ (C≡N); nmr δ 3.28 (q, 1 H, $CHCH_3$, $J$ = 7 Hz), 1.53 (s, 3 H, $CCH_3$), and 1.4–0.8 (m, 11 H, $CHCH_3$, two $CH_2CH_2$); mass spectrum $M^+$ = 371. *Anal.* ($C_{25}H_{25}NO_2$) C, H, N.

The remainder of the oil was refluxed in 15% aqueous ethanolic KOH for 3 hr and worked up (as for **8**) to give **12** (215 mg), mp 89–91°.

**Method B.** The ester **18** (2.8 g, 0.012 mol, prepared from **8** *via* **17**) was heated at reflux in 15% aqueous ethanolic KOH for 3 hr and worked up, as above, to give crude **12** (2.48 g, 94%). Three recrystallizations (hexane) afforded pure **12** (1.66 g, 62.5%), mp 91.5–93°. *Anal.* ($C_{12}H_{14}O_3$) C, H.

**Bis[p-(cyclopropylcarbonyl)-α-methylbenzyl]amine (14).** A solution of **10** (600 mg, 2.37 mmol) in DMSO (3 ml) was added to a slurry of $NH_4Cl$ (129 mg, 2.41 mmol) and NaCN (120 mg, 2.45 mmol) in DMSO (5 ml) at ambient temperature, and the mixture was warmed and held at 70° overnight. The mixture was cooled, diluted with $H_2O$ (15 ml), and extracted (50:50 $Et_2O$–hexane). The extract was dried and concentrated, and the crude product was obtained by preparative tlc (silica gel, 2:3 EtOAc–hexane), followed by removal of a volatile impurity (which was not sufficiently separated by tlc because of similar polarity) *in vacuo* at 100°: ir (KBr) 3370 (NH), 1675 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 8.1–7.0 (m, 8 H, ArH), 3.78, 3.49 (2 q, 2 H, two $CHCH_3$, $J$ = 6.5 Hz), 2.8–2.2 (m, 2 H, two CHC=O), 1.57 (s, 1 H, NH), and 1.5–0.7 (m, 14 H, two $CH_2CH_2$ and two $CHCH_3$). *Anal.* Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 78.61; H, 6.50; N, 3.64.

**Tris[p-(cyclopropylcarbonyl)benzyl]amine (15).** To a cooled (ice bath), stirred slurry of $NH_4Cl$ (3.27 g, 0.062 mol) and NaCN (3.04 g, 0.062 mol) in DMF (100 ml) was added a solution of **6** (13.3 g, 0.056 mol) in DMF (100 ml) over a period of 1 hr. The stirred solution was allowed to warm to room temperature overnight, after which time additional $NH_4Cl$ (0.654 g, 0.012 mol) and NaCN (0.608 g, 0.012 mol) were added. After 24 hr at room temperature, the reaction was worked up as described for **7**. The crude product (9.0 g) was extracted with hot hexane (4 l.) which, upon cooling, afforded **15** (4.7 g, 55%): mp 181–183°; nmr δ 7.96, 7.47 (2 d, 12 H, three ArH, $J$ = 8 Hz), and 3.60 (s, 6 H, three $CH_2N$); mass spectrum $M^+$ = 491. *Anal.* ($C_{33}H_{33}NO_3$) C, H, N.

**Methyl p-(Cyclopropylcarbonyl)hydratropate (18).** Compound **8** was esterified ($CH_2N_2$–$Et_2O$) and the oily ester **17** was distilled, bp 130–135° (0.5 mm). *Anal.* ($C_{13}H_{14}O_3$) C, H.

To a stirred suspension of $NaNH_2$ (545 mg, 14 mmol) in anhydrous $NH_3$ (150 ml) in a cooled (Dry Ice) flask was added a solution of **17** (2.18 g, 10 mmol) in $Et_2O$ (5 ml). After 0.5 hr, a solution of MeI (3.25 g, 22.8 mmol) in $Et_2O$ (5 ml) was added. The solution was then allowed to reflux (Dry Ice condenser) for 1 hr; then the $NH_3$ was allowed to evaporate overnight. The residual oil was diluted with $Et_2O$ (100 ml) and washed ($H_2O$, saturated aqueous $NaHCO_3$, and saturated brine). The $Et_2O$ fraction was dried and concentrated to give **18** (2.83 g, 95%). *Anal.* ($C_{14}H_{16}O_3$) C, H.

**p-(Cyclopropylmethyl)hydratropic Acid (19) and Sodium p-(Cyclopropylmethyl)hydratropate (20).** Compound **12** (1.0 g, 4.6 mmol) was reduced by the method previously described for the preparation of **1** to afford 830 mg of crude product. Column chromatography (silica gel, elution with benzene) afforded **19** (660 mg, 71%), bp 125° (0.05 mm). *Anal.* ($C_{13}H_{16}O_2$) C, H.

The sodium salt of **19** was prepared as above to give **20**, mp 164–167°. *Anal.* ($C_{13}H_{15}O_2Na$) C, H, Na.

**p-(Cyclopropylmethyl)phenethyl Alcohol (23).** A solution of **1** (3.0 g, 15.8 mmol) in THF (25 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.5 g, 39.5 mmol) in THF (25 ml) at a rate sufficient to maintain gentle reflux; then the solution was heated at reflux overnight. Excess $LiAlH_4$ was destroyed (dilute $H_2SO_4$) and the mixture was extracted ($Et_2O$). The extract was washed (10% $NaHCO_3$ and $H_2O$), dried, and concentrated. Vacuum distillation of the residue gave **23** (2.6 g, 93%), bp 88–89° (0.05 mm). *Anal.* ($C_{12}H_{16}O$) C, H.

**p-(Cyclopropylhydroxymethyl)phenethyl Alcohol (24).** Compound **8** (2.0 g, 9.5 mmol) was reduced by the procedure described for the preparation of **23** to give a crude solid material (1.51 g). Crystallization (EtOAc–hexane) gave **23** (1.19 g, 63%), mp 92.5–93°. *Anal.* ($C_{12}H_{16}O_2$) C, H.

**(α-Cyclopropyl-α-hydroxy-p-tolyl)acetic Acid (25).** A solution of **17** (2.14 g, 9.4 mmol) in MeOH (35 ml) was added dropwise to a stirred suspension of $NaBH_4$ (1.02 g, 28.2 mmol) in MeOH (20 ml). After 2 hr, excess $NaBH_4$ was destroyed (dilute $H_2SO_4$) and MeOH was removed *in vacuo*. The residue was diluted ($H_2O$) and extracted ($CHCl_3$), and the extract was dried and concentrated to give a viscous oil (2.03 g). The oil was heated at reflux for 3 hr in 15% aqueous ethanolic KOH. The product was isolated in the usual way and crystallized (EtOAc–hexane) to give **25** (1 g, 49.5%), mp 95.5–96.5°. *Anal.* ($C_{12}H_{14}O_3$) C, H.

The base-insoluble fraction afforded a small amount of diol **24** (215 mg, 11%), mp 90–92°.

**2-[p-(Cyclopropylcarbonyl)phenyl]acetohydroxamic Acid (26).** To a cooled (ice bath) methanolic solution of $NH_2OH$ [prepared at 40° from $NH_2OH \cdot HCl$ (1.94 g, 28 mmol) in MeOH (15 ml) and KOH (2.7 g, 41 mmol) in MeOH (8 ml)] was added **17** (3.0 g, 13.7 mmol) with vigorous stirring. The solution was immediately filtered and the pale-yellow filtrate was allowed to stand for 5 hr. The crystals were collected and heated with dilute AcOH (1 equiv). After cooling, the product was collected and recrystallized (EtOAc) to give **26** (1.72 g, 57%), mp 155–157°. *Anal.* ($C_{12}H_{13}NO_3$) C, H, N.

**2-[p-(Cyclopropylcarbonyl)phenyl]acetamide (28).** Anhydrous $NH_3$(g) was delivered into a cooled (ice bath), well-stirred solution (benzene) of the acid chloride **27** [prepared from the acid **8** (1.0 g, 4.9 mmol) and oxalyl chloride (2.5 *M* excess) in benzene at room temperature (24 hr); solvent and excess oxalyl chloride were removed *in vacuo* (<30°) and the acid chloride was used without purification]. After 15 min, $H_2O$ was added and the organic layer was separated, washed (10% aqueous $NaHCO_3$ and $H_2O$), dried, and concentrated. The crude solid product was crystallized (DMSO–$H_2O$) to give **28** (850 mg, 85%), mp 171–172°. *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

**Isopropyl p-(Cyclopropylcarbonyl)phenylacetate (29).** To a solution (benzene) of **27** [prepared from **8** (650 mg, 3.2 mmol)] was added *i*-PrOH (4 ml). After 24 hr at room temperature, the solution was diluted ($CHCl_3$), washed (10% aqueous $NaHCO_3$ and $H_2O$), dried, and concentrated. Crystallization (MeOH–$H_2O$) of the amber liquid afforded **29** (650 mg, 83%), mp 58–60°. *Anal.* ($C_{15}H_{18}O_3$) C, H.

**2-Dimethylaminoethyl p-(Cyclopropylcarbonyl)phenylacetate Hydrochloride (30).** To a solution (benzene) of **27** [prepared from **8** (500 mg, 2.45 mmol)] was added a solution (PhH) of pyridine (194 mg, 2.45 mmol) and 2-dimethylaminoethanol (237 mg, 2.66 mmol) at room temperature. The mixture was heated at reflux for 45 min and then stirred at room temperature overnight. The solution was diluted ($CHCl_3$) and extracted (25 ml of $H_2O$ containing 3 ml of 1 *N* HCl). The aqueous layer was neutralized (solid $NaHCO_3$) and extracted ($CHCl_3$); the extract was dried, treated with Darco, and concentrated to afford a clear oil. A solution ($Et_2O$) of the oil was

treated with 3 *N* MeOH–HCl (0.5 ml) to afford **30** (306 mg, 40%), mp 140.5–142.5°. *Anal.* ($C_{16}H_{21}NO_3$·HCl) C, H, N, Cl.

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# 4- and 5-Aryl-1-naphthaleneacetic Acids as Antiinflammatory Agents

James S. Kaltenbronn

*Chemistry Department, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.*
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A series of 4- and 5-aryl-1-naphthaleneacetic acids has been prepared and its antiinflammatory activity investigated. Among its 29 members are several which are among the most potent compounds yet reported. As measured by the anti-uv-erythema test, the most potent compound is 4-phenyl-1-naphthaleneacetic acid **(8)** with a potency 62 times that of phenylbutazone. Measured by the cotton-pellet antigranulation test, the most potent compound is (+)-α-methyl-5-phenyl-1-naphthaleneacetic acid **(34)**, whose potency is 46 times that of phenylbutazone.

Among the reports of compounds exhibiting antiinflammatory activity which have appeared in recent years,[1] a number describe compounds which belong to the general class of arylacetic acids. Our own research in this area has led to the synthesis of a series of 4- and 5-aryl-1-naphthaleneacetic acids which exhibit this activity. As measured by the anti-uv-erythema test,[2] the potency of several members is among the highest yet reported.[3]

**Chemistry.** The compounds were prepared according to Scheme I. When 4- or 5-methyl-1-tetralone **(1b,c)** was the starting point of the sequence, the side chain was eventually functionalized using NBS. When 1-tetralone **(1a)** was the starting point, a functionalized side chain was eventually added *via* the chloromethylation technique. Chloromethylation of 1-arylnaphthalenes containing aryl groups which are not highly activated leads to substitution in the 4 position of the naphthalene nucleus and thus can be used only to prepare 4-aryl-1-naphthaleneacetic acids. This technique was also necessary in those cases where the aryl group bore an alkyl substituent which would compete in the subsequent NBS reaction.

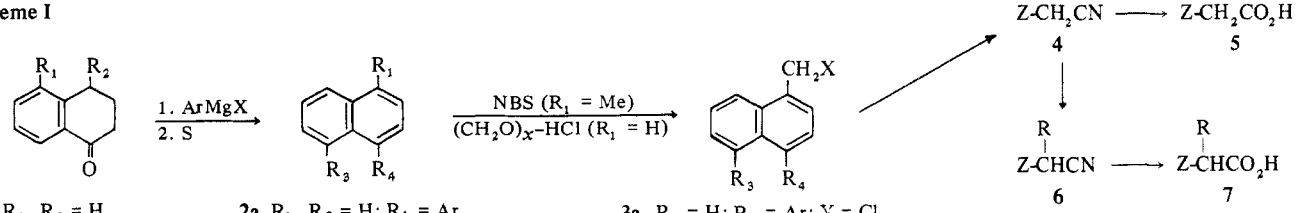
In those cases where the nitrile was to be alkylated, the nitrile was purified, either by recrystallization or by chromatography on neutral alumina. Since unalkylated material proved to be difficult to separate from monoalkylated products, the alkylation was carried out using a 15% excess of NaH, ensuring that no unalkylated material was present. Subsequent basic hydrolysis proceeded only as far as the amide stage with any dialkylated material, enabling an easy separation from monoalkylated acid. However, when the α-alkyl group became large, an acid hydrolysis became necessary (compounds **27** and **28**).

The position of chloromethylation was proven to be as depicted in Scheme I in two cases (compounds **8** and **13**). These compounds were prepared both by the chloromethylation procedure and by the NBS method starting from 4-methyl-1-tetralone **(1b)**, a method which leads to an unambiguous structural assignment. The respective products obtained by both methods were identical. By analogy the other compounds prepared by the chloromethylation technique (compounds **17–19**) are presumed to have the 4-aryl-1-naphthaleneacetic acid structure.

In preparing the *o*-fluorophenyl derivatives from 1-bromo-2-fluorobenzene, it was necessary to use low-temperature lithium exchange to prevent extensive benzyne formation.[4,5]

**Pharmacology.** Compounds were screened for their ability to suppress the erythema developing in albino guinea pig skin 2 hr after a standard exposure to ultraviolet irradiation using Winder's modification[2] of Wilhelmi's method.[6] All agents were administered by gavage to depilated guinea pigs. Responses to treatment on an all-or-non basis were compared for test drug ($N = 5$) and the phenylbutazone reference dose ($N = 10$) or vehicle ($N = 10$). The significance of treatment contrasts was determined by reference to tables of ready-computed probabilities.[7] Com-

**Scheme I**




**1a**, $R_1$, $R_2$ = H
b, $R_1$ = H; $R_2$ = Me
c, $R_1$ = Me; $R_2$ = H

**2a**, $R_1$, $R_3$ = H; $R_4$ = Ar
b, $R_1$ = Me; $R_3$ = H; $R_4$ = Ar
c, $R_1$ = Me; $R_3$ = Ar; $R_4$ = H

**3a**, $R_3$ = H; $R_4$ = Ar; X = Cl
b, $R_3$ = H; $R_4$ = Ar; X = Br
c, $R_3$ = Ar; $R_4$ = H; X = Br

Z = the 4- or 5-aryl-1-naphthyl group
R = alkyl