L-**Aspartyl-L-*m,p*-dimethoxyphenylalanine Methyl Ester (20).** The coupling reaction followed general procedure B. The residue obtained from removal of the solvent under reduced pressure was crystallized from isopropyl alcohol to give *N*-(benzyloxycarbonyl)-β-benzyl-L-aspartyl-L-*m,p*-dimethoxyphenylalanine methyl ester as a white solid (61%): mp 154–155 °C; $[\alpha]^{25}_D$ +41.4° (*c* 1.0, $CHCl_3$). Anal. ($C_{31}H_{34}N_2O_9$) C, H, N.

The deprotection reaction followed general procedure D. Removal of the solvent under reduced pressure yielded **20** as a white solid (98%): mp 139–140 °C; $[\alpha]^{25}_D$ −1.2° (*c* 1.2, CH_3OH). Anal. ($C_{16}H_{22}N_2O_7$) C, H, N.

Acknowledgment. We acknowledge the Food and Drug Administration (Grant FD 00590) for their support of this investigation. M.K. thanks the Mitsubishi-Kasei Institute of Life Sciences for enabling him to perform this work. We also thank Constance Mullin for her help in preparing this manuscript.

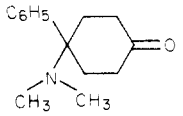
4-Amino-4-arylcyclohexanones and Their Derivatives, a Novel Class of Analgesics. 1. Modification of the Aryl Ring

Daniel Lednicer,[1] Philip F. VonVoigtlander,* and D. Edward Emmert

The Upjohn Company, Research Laboratories, Kalamazoo, Michigan 49001. *Received August 7, 1979*

Investigation of central nervous system activity of phenylcyclohexylamines was continued by preparation of "reversed" analogues. Following the unexpected finding of analgesic activity with 1-(dimethylamino)-1-phenylcyclohexylamine, the SAR of the series was investigated. Synthesis starts by double Michael reaction of acrylate on arylacetonitriles. Following cyclization, decarboxylation, ketalization, and saponification, the geminally substituted acid is rearranged to the isocyanate by means of $(C_6H_5O)_2PON_3$. Isocyanates were then converted to the title compounds. Analgesic activity is very sensitive to the nature and position of the substitutent on the aromatic ring. The most potent compounds in this series (*p*-CH_3, *p*-Br) showed 50% the potency of morphine. Deletion of the ring oxygen abolishes activity.

Compounds related to 4-phenylcyclohexylamine have proven a fruitful nucleus for the preparation of biologically active compounds. Suitable modifications of this moiety have provided several series of compounds which show neuroleptic activity;[2] substitution of a carbon onto the ring atom bearing aryl leads to hypotensive agents.[3] One of the more interesting of the earlier series was that in which that same carbon bore an oxygen substituent.[2] It was thus of some interest to ascertain the effect on biological activity of placing a nitrogen atom on that apparently important position. Specifically, we undertook the preparation of 4-phenyl-4-(dimethylamino)cyclohexanone (1). Random

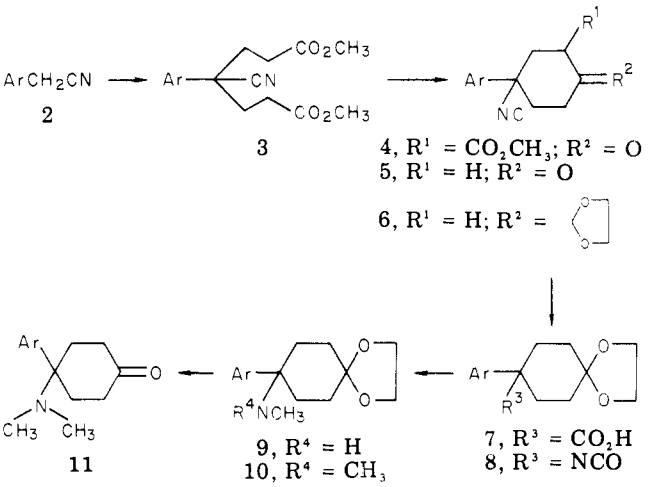


1

screening surprisingly showed this compound to exhibit narcotic-like analgesic activity. This was particularly unanticipated because the molecule departs so radically from the various SAR correlations proposed for centrally acting analgesics.[4] We thus undertook the systematic investigation of the SAR in this series. The present report deals with the effect on activity of modification of the aromatic moiety.

Chemistry. Our initial approach to these deceptively simple compounds relied heavily on the scheme we had devised in connection with the earlier work for construction of the substituted carboxylic acids (**7**) (Scheme I).[3] This route offered the advantage that most of the required arylacetonitriles are commercially available (the *p*-*tert*-butylnitrile was obtained in a straightforward manner from the benzyl alcohol). The key to the sequence was the

Scheme I

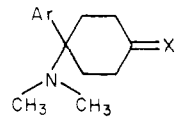


recently developed modification of the Curtius reaction which allows this transformation to be carried out in the presence of acid-labile groups.[5] We modified this procedure yet further in that we substituted an inert high-boiling solvent (anisole) for the alcohols used in the original work. It is a tribute to the extreme steric hindrance about the quaternary carbon that the isocyanates (**8**) obtained by this reaction sequence are usually stable to chromatography on silica gel—the routine isolation procedure. For reasons which are not immediately apparent, the product from the acid containing the 2-thienyl group as the aromatic substituent showed the expected isocyanate reactivity; in this case, the reaction was run in ethanol to afford the corresponding carbamate. Reduction of **8** by means of $LiAlH_4$ afforded the secondary amine (**9**). This was then methylated by means of CH_2O and $NaBH_4$[6] (the hindered nature of the amine again manifested itself in the observation that at least one recycle was required to assure complete

(1) Address: Mead Johnson & Co., Evansville, Indiana 47721.
(2) See, for example, D. Lednicer, D. E. Emmert, R. A. Lahti, and A. D. Rudzik, *J. Med. Chem.*, 16, 1251 (1973).
(3) D. Lednicer, D. E. Emmert, A. D. Rudzik, and B. E. Graham, *J. Med. Chem.* 18, 593 (1975).
(4) (a) O. Schauman, *Pharmazie*, 4, 364 (1949); (b) A. H. Beckett and A. F. Casey, *J. Pharm. Pharmacol.*, 6, 986 (1954); (c) P. S. Portoghese, *J. Pharm. Sci.*, 55, 865 (1966).
(5) T. Shioivi, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 94, 6204 (1972).
(6) B. L. Sondergam, J. Hentchoya, H. Charle, and G. Charles, *Tetrahedron Lett.*, 261 (1973).

0022-2623/80/1823-0424$01.00/0

Table I. Analgesic Activity



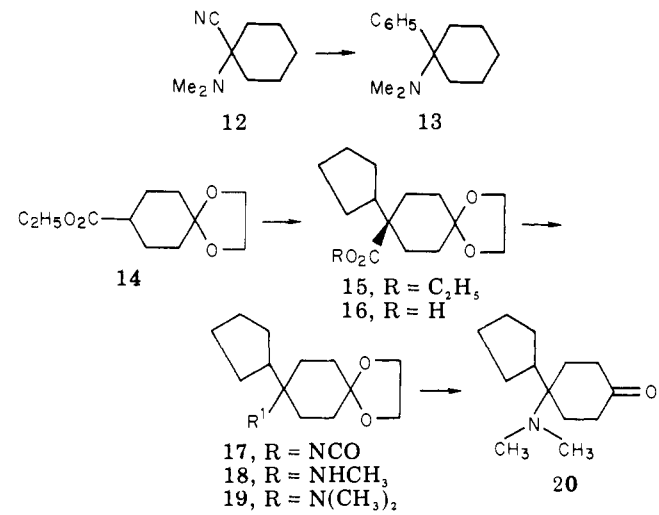
no.	Ar	X	analgesic act.:[a] ED_{50}, mg/kg[b] flick	pinch	screen	writhe	antag
11a	C_6H_5	O	71	66	>100	44	>100
10a	C_6H_5	OCH_2CH_2O	>100	>100	>100	>100	>100
11b	2-thienyl	O	63	63	>100	32	>100
10b	2-thienyl	OCH_2CH_2O	24	47	>100	22	>100
11c	1-naphthyl	O	>100	>100	>100	>100	>100
10c	1-naphthyl	OCH_2CH_2O	>100	>100	>100	>100	>100
11d	o-$CH_3C_6H_4$	O	63	63	>100	63	>100
10d	o-$CH_3C_6H_4$	OCH_2CH_2O	>100	>100	>100	22	>100
11e	m-$CH_3C_6H_4$	O	71	79	>100	56	>100
10e	m-$CH_3C_6H_4$	OCH_2CH_2O	>100	>100	>100	>100	>100
11f	p-$CH_3C_6H_4$	O	1	4	>50	3	>50
10f	p-$CH_3C_6H_4$	OCH_2CH_2O	3	2	>25	2	>25
11g	m-$(CH_3O)C_6H_4$	O	>100	71	>100	47	>100
10g	m-$(CH_3O)C_6H_4$	OCH_2CH_2O	81	29	>100	17	>100
11h	p-$(CH_3O)C_6H_4$	O	19	20	>25	19	>25
11i	3,4-$(CH_3O)_2C_6H_3$	O	>25	>25	>25	>25	>25
10i	3,4-$(CH_3O)_2C_6H_3$	OCH_2CH_2O	87	71	>100	71	>100
11j	p-FC_6H_4	O	44	44	>50	10	>50
10j	p-FC_6H_4	OCH_2CH_2O	35	13	>25	15	>25
11k	o-ClC_6H_4	O	22	35	>100	20	>100
10k	o-ClC_6H_4	OCH_2CH_2O	71	71	>100	71	>100
11l	m-ClC_6H_4	O	>100	>100	>100	>100	>100
10l	m-ClC_6H_4	OCH_2CH_2O	>100	>100	>100	71	>100
11m	p-ClC_6H_4	O	8	9	>25	3	>25
10m	p-ClC_6H_4	OCH_2CH_2O	4	3	>25	4	>25
11n	p-BrC_6H_4	O	4	5	>100	2	>100
10n	p-BrC_6H_4	OCH_2CH_2O	3	3	>100	1	>100
11o	3,4-$(Cl)_2C_6H_3$	O	63	63	>100	>100	>100
10o	3,4-$(Cl)_2C_6H_3$	OCH_2CH_2O	>100	>100	>100	>100	>100
11p	2,4-$(Cl)_2C_6H_3$	O	>100	>100	>100	71	>100
10p	2,4-$(Cl)_2C_6H_3$	OCH_2CH_2O	25	25	>100	10	>100
11q	p-$[(CH_3)_3C]C_6H_4$	O	>100	>100	>100	>100	>100
10q	p-$[(CH_3)_3C]C_6H_4$	OCH_2CH_2O	>100	>100	>100	>100	>100
meperidine hydrochloride			22	29	>100	15	>100
morphine sulfate			1.5	1.6	>100	0.6	>100
pentazocine lactate			7	6	>50	4	>50

[a] The upper and lower 95% confidence intervals (ref 10) were not more than 2 and 0.5 times the ED_{50}, respectively. [b] See Experimental Section and ref 8 for description of methods.

reaction). Finally, prolonged exposure to acid gave the free ketals. It is of interest in this connection that the feared elmination of the tertiary benzylic amine was never observed under the admittedly mild conditions used.

In order to ascertain the role of the oxygen at the 4 position, the deoxy counterpart (**13**) of the lead compound was prepared in a straightforward manner by displacement of the cyano group from the β-aminonitrile of cyclohexanone (**12**) by means of phenylmagnesium bromide (Scheme II).[7] The necessity for the aromatic portion was tested by replacing this group with a cyclopentyl ring. Thus, alkylation of the anion from **14** (LDA) with cyclopentyl bromide gave **15** in workable yield. The ester was then saponified and the acid taken on to the dimethylamine analogue **20** by the same sequence as that used in the main series.

Scheme II



Results

The ED_{50} values for these compounds are recorded in Table I. The ketals and ketone analogues were of similar potency. Substitution on the aromatic ring has a pronounced effect on activity in this series. A substantial enhancement of potency is seen by inclusion of a substituent in the para position. Ortho and meta substitution give agents with moderate activity. At first sight, the rank order of activity ($CH_3 \cong Br > Cl > CH_3O > F > H$) is suggestive of some steric effect; it is of note in this connection that the *p-tert*-butyl compound is inert in this

(7) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, 24, 46 (1954).

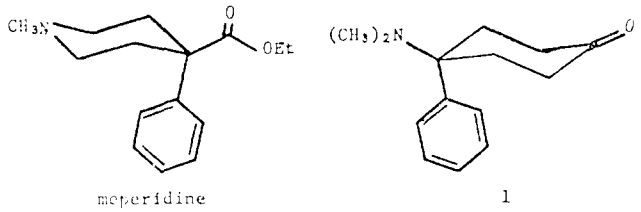


Figure 1.

assay at the top screening dose. It is of note, too, that all compounds reported in Table I are devoid of sedative (screen) as well as morphine antagonistic (antag) activity. Two compounds (**13** and **20**) not listed in Table I were inactive on all five of the end points.

Further work on selected analogues shows these agents to be classical opioids.[8] Effects of these compounds can, for example, be reversed by administration of naloxone. We consider this at least presumptive evidence that these interact with the same receptors as do classical narcotics. This observation is at first sight surprising, since the compounds in question differ markedly from the connectivity posited by Beckett and Casey. Closer examination, however, shows topological similarity to the prototype narcotic meperidine. Comparison of Dreiding models of 1 and meperidine, wherein the phenyl groups are axially disposed,[9] allows direct superposition of carbonyl oxygens and nitrogen (N to O distance is 5 Å in each compound). It is of note that the aromatic rings will then occupy the same plane with about 0.5 Å separation (Figure 1). While it is tempting to adduce physical significance to this observation, more detailed data is needed regarding the molecular pharmacology of these compounds. The topological coincidence does, however, serve to rationalize the activity of the above agents.

Experimental Section

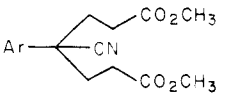
All melting points are uncorrected and reported as observed on a Thomas-Hoover melting point apparatus. The authors are indebted to the Department of Physical and Analytical Research of The Upjohn Co. for spectral and elemental analyses. Analytical results indicated by element symbols were within ±0.4% of theory.

***p*-*tert*-Butylphenylacetonitrile.** A solution of 5 mL of thionyl chloride in 10 mL of benzene was added to 10.0 g (0.061 mol) of *p*-*tert*-butylbenzyl alcohol in 85 mL of benzene. Following 30 min of stirring at room temperature, the mixture was heated to reflux for 4 h. The mixture was allowed to cool, and the solvent was removed under vacuum. The residue was distilled at 0.05 mm to afford 10.14 g (92%) of product, bp 62–65 °C.

A mixture of 9.64 g (0.053 mol) of the benzyl chloride obtained above, 10.13 g of potassium cyanide, and 0.10 g of potassium iodide in 71 mL of water and 150 mL of methanol was heated at reflux for 1 h. The bulk of the methanol was removed under vacuum and the residue extracted with ether. The organic layer was washed with water and brine and taken to dryness. Distillation of the residual oil at 0.03 mm afforded 6.38 g (70%) of product, bp 79–84 °C. Anal. ($C_{12}H_{21}N$) H, N; C: calcd, 83.19; found, 82.56.

Dimethyl 4-Aryl-4-cyanopimelates (Table II). A mixture of 0.10 mol of the appropriate arylacetonitrile, 47 mL of methyl acrylate, and 60 mL of *tert*-butyl alcohol was brought to reflux. The source of heat was removed and there was added quickly 15.2 mL of Triton B in 23 mL of *tert*-butyl alcohol. Following 4 h of heating at reflux, the mixture was allowed to cool and diluted with water and benzene. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was distilled first at 40 mm to remove excess reagent; the pressure was then reduced and the product allowed to distill over. These esters were characteristically very viscous oils and were, as a rule, not characterized further.

Table II. Dimethyl 4-Aryl-4-cyanopimelates[a]



no.	Ar	yield, %	bp (mmHg), °C
3b	2-thienyl	73	162–180 (0.05)
3d	*o*-$CH_3C_6H_4$	37	168–175 (0.03)
3e	*m*-$CH_3C_6H_4$	66	165–174 (0.04)
3f	*p*-$CH_3C_6H_4$	73	170–180 (0.07)
3g	*m*-$(CH_3O)C_6H_4$	56	180–187 (0.08)
3k	*o*-ClC_6H_4	73	170–183 (0.08)
3l	*m*-ClC_6H_4	64	175–181 (0.04)
3n	*p*-BrC_6H_4	70	183–193 (0.04)
3o	3,4-$(Cl)_2C_6H_3$	70	187–196 (0.04)
3p	2,4-$(Cl)_2C_6H_3$	66	183–184 (0.04)
3q	*p*-$[(CH_3)_3C]C_6H_4$	70	180–199 (0.05)

[a] All products were viscous oils; none were subjected to combustion analyses.

4-Aryl-4-cyano-2-carbomethoxycyclohexanones (Table III). Solid potassium *tert*-butoxide (22.5 g, 0.20 mol) was added to a solution of 0.10 mol of the cyanopimelate in 700 mL of THF. The mixture was heated at reflux for 5 h, cooled in ice, and treated with 170 mL of 2.5 N acetic acid. The organic layer was separated, diluted with benzene, and washed in turn with aqueous sodium bicarbonate, water, and brine. The solid which remained when the organic solution was taken to dryness was recrystallized. In those cases where the product failed to crystallize, it was used directly in the next step.

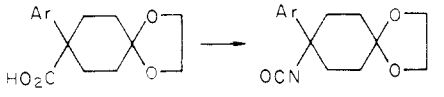
4-Aryl-4-cyanocyclohexanones (Table IV). A mixture of 0.100 mol of the carbomethoxycyclohexanone, 310 mL of 10% aqueous sulfuric acid, and 720 mL of acetic acid was stirred on a steam bath for 24 h. The mixture was then allowed to cool, diluted with water, and extracted thoroughly with ether. The organic layer was washed with water, aqueous sodium bicarbonate, and brine. The solid which remained when the extract was taken to dryness was then recrystallized.

In several cases the product crystallized on dilution of the reaction mixture. The solid was then collected on a filter and recrystallized.

4-Aryl-4-cyanocyclohexanone Ethylene Ketals (Table V). A mixture of 0.050 mol of the cyano ketone, 3.6 mL of ethylene glycol, and 0.16 g of *p*-toluenesulfonic acid in 140 mL of benzene was stirred at reflux under a Dean–Stark trap for 6 h. The solution was allowed to cool, washed with aqueous sodium bicarbonate, and taken to dryness. The residual solid was then recrystallized.

4-Aryl-4-carboxycyclohexanones Ethylene Ketals (Table VI). A mixture of 0.070 mol of the cyano ketal and 15.0 g (0.38 mol) of sodium hydroxide in 150 mL of ethylene glycol was stirred at reflux for 18 h. The mixture was allowed to cool, diluted with ice–water, and covered with ether. Hydrochloric acid was then added slowly with continuous stirring until the aqueous layer was strongly acidic. The organic layer was separated, washed with water and brine, and taken to dryness. The residual solid was purified by recrystallization.

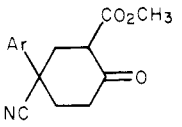
4-Aryl-4-isocyanatocyclohexanone Ethylene Ketals (Table VII). To a mixture of 0.040 mol of the appropriate 4-aryl-4-carboxycyclohexanone ethylene ketal and 5.6 g of triethylamine in 100 mL of anisole was added 11.17 g of diphenyl phosphonic azide. The mixture was then warmed to 90 °C in an ice bath (effervescence was noted at 80 °C). At the end of 2 h the solvent was removed by means of a mechanical vacuum pump. The total residue was chromatographed as quickly as possible on silica gel. The isocyanate (ν_{max} 2250–2270 cm^{-1}) thus obtained was recrystallized when a solid. When an oil, the product was reduced without further purification.



(8) D. Lednicer and P. F. VonVoigtlander, *J. Med. Chem.*, **22**, 1157 (1979).

(9) The phenyl ring in a closely related compound has been determined by NMR and X-ray diffraction to occupy the axial position. D. Lednicer and D. J. DuChamp, *J. Org. Chem.*, **39**, 2311 (1974).

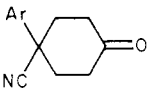
Table III. 4-Aryl-4-cyano-2-carbomethoxycyclohexanones



no.	Ar	rxn solvent	mp, °C	yield, %	formula
4b	2-thienyl	Et_2O-PE	76-78	90	$C_{13}H_{13}NO_3S$
4d	o-$CH_3C_6H_4$		107-113[a]	93	
4e	m-$CH_3C_6H_4$	Et_2O	126.5-128	90	$C_{16}H_{17}NO_3$
4f	p-$CH_3C_6H_4$	*b*		99	
4g	m-$(CH_3O)C_6H_4$	*b*		99	
4k	o-ClC_6H_4	*a*	113-118	95	
4l	m-ClC_6H_4	CH_2Cl_2-SSB	123-125	76	$C_{15}H_{14}ClNO_3$
4n	p-BrC_6H_4	Me_2CO-SSB	164-166	67	$C_{15}H_{14}BrNO_3$
4o	3,4-$(Cl)_2C_6H_3$	Et_2O	82-87[c]	95	$C_{15}H_{13}Cl_2NO_3$
4p	2,4-$(Cl)_2C_6H_3$	*b*		95	
4q	p-[$(CH_3)_3C$]C_6H_4	Et_2O-PE	108-110	78	$C_{19}H_{23}NO_3$

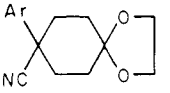
[a] Could not be satisfactorily recrystallized. [b] Amorphous gum. [c] Analytical sample melted at 112-113 °C.

Table IV. 4-Aryl-4-cyanocyclohexanones



no.	Ar	rxn solvent	mp, °C	yield, %	formula
5b	2-thienyl	CH_2Cl_2-SSB	117.5-119	66	$C_{11}H_{11}NOS$
5d	o-$CH_3C_6H_4$	Et_2O-SSB	86.5-89	78	$C_{14}H_{15}NO$
5e	m-$CH_3C_6H_4$	Et_2O-PE	51-54	76	$C_{14}H_{15}NO$
5f	p-$CH_3C_6H_4$	Et_2O-PE	79-82	74	$C_{14}H_{15}NO$
5g	m-$(CH_3O)C_6H_4$	Et_2O	72-76	64	$C_{14}H_{15}NO_2$
5k	o-ClC_6H_4	CH_2Cl_2-SSB	106-108	80	$C_{13}H_{12}ClNO$
5l	m-ClC_6H_4	PE	71-73.5	54	$C_{13}H_{12}ClNO$
5n	p-BrC_6H_4	CH_2Cl_2-SSB	110-113	70	$C_{13}H_{12}BrNO$
5o	3,4-$(Cl)_2C_6H_3$	CH_2Cl_2-SSB	156-157.5	58	$C_{13}H_{11}Cl_2NO$
5p	2,4-$(Cl)_2C_6H_3$	CH_2Cl_2-SSB	119-122.5	54	$C_{13}H_{11}Cl_2NO$
5q	p-[$(CH_3)_3C$]C_6H_4	CH_2Cl_2-SSB	141-143	78	$C_{17}H_{21}NO$

Table V. 4-Aryl-4-cyanocyclohexanone Ethyl Ketals



no.	Ar	rxn solvent	mp, °C	yield, %	formula
6b	2-thienyl	C_6H_{12}[a]	90.5-92	90	$C_{13}H_{15}NO_2S$
6d	o-$CH_3C_6H_4$	Et_2O-PE	65.5-68.5	85	$C_{16}H_{19}NO_2$
6e	m-$CH_3C_6H_4$	PE	36.5-38	61	$C_{16}H_{19}NO_2$
6f	p-$CH_3C_6H_4$	C_6H_{12}	107.5-110	92	$C_{16}H_{19}NO_2$
6g	m-$(CH_3O)C_6H_4$	SSB	70-72	92	$C_{16}H_{19}NO_3$
6k	o-ClC_6H_4	C_6H_{12}	98.5-101	89	$C_{15}H_{16}ClNO_2$
6l	m-ClC_6H_4	Et_2O-PE	68-71	91	$C_{15}H_{16}ClNO_2$
6n	p-BrC_6H_4	C_6H_{12}	127-131	96	$C_{15}H_{16}BrNO_2$
6o	3,4-$(Cl)_2C_6H_3$	C_6H_{12}	120.5-123	96	$C_{15}H_{16}Cl_2NO_2$
6p	2,4-$(Cl)_2C_6H_3$	CH_2Cl_2-SSB	109.5-112	91	$C_{15}H_{15}Cl_2NO_2$
6q	p-[$(CH_3)_3C$]C_6H_4	C_6H_{12}	124-125.5	89	$C_{19}H_{25}NO_2$

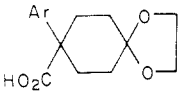
[a] Cyclohexane.

Rearrangement of the 2-Thienyl Acid 8b in EtOH. To a solution of 2.68 g (0.010 mol) of 4-carboxy-4-(2-thienyl)cyclohexanone ethylene ketal and 1.39 mL of triethylamine in 40 mL of ethanol there was added 2.75 g of diphenyl phosphonic azide. Following 5 h of heating the solution at reflux, the bulk of the solvent was removed under vacuum. The residue was dissolved in water and ether–benzene. The organic layer was washed, in turn, with water, ice-cold 2.5 N hydrochloric acid–water, saturated sodium bicarbonate, and brine and taken to dryness. The residual solid was recrystallized from cyclohexane to give 1.58 g (51%) of product, mp 113–117 °C. Anal. ($C_{15}H_{21}NO_4S$) C, H, N.

4-Aryl-4-(methylamino)cyclohexanone Ethylene Ketal Hydrochlorides (Table VIII). A solution of 0.29 mol of the 4-aryl-4-isocyanatocyclohexanone ethylene ketal in 140 mL of THF was added to a well-stirred suspension of 1.67 g of lithium aluminum hydride in 13 mL of THF. The mixture was heated at reflux for 4 h and then cooled in ice. There were added, in turn, 1.7 mL of water, 1.7 mL of 15% aqueous sodium hydroxide, and 5.1 mL of water. The inorganic gel was collected on a filter and the filtrate taken to dryness. A solution of the residue in ether was then treated with a just sufficient amount of 3 N ethereal hydrogen chloride to precipitate all the amine. The solid was recrystallized from methylene chloride–ethyl acetate. In those few cases where the free base was crystalline, this product was recrystallized directly.

4-Aryl-4-(dimethylamino)cyclohexanone Ethylene Ketals

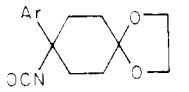
Table VI. 4-Aryl-4-carboxycyclohexanone Ethylene Ketals



no.	Ar	rxn solvent	mp, °C	yield, %	formula
7b	2-thienyl	CH_2Cl_2-SSB	125-127	82	$C_{13}H_{16}O_4S$
7d	*o*-$CH_3C_6H_4$	CH_2Cl_2-SSB	174-177	63	$C_{16}H_{20}O_4$
7e	*m*-$CH_3C_6H_4$	CH_2Cl_2-SSB	152-154	84	$C_{16}H_{20}O_4$
7f	*p*-$CH_3C_6H_4$	CH_2Cl_2-SSB	172-174	85	$C_{16}H_{20}O_4$
7g	*m*-$(OCH_3)C_6H_4$		102-107[a]	99	
7k	*o*-ClC_6H_4	CH_2Cl_2-SSB	195-197	77	$C_{15}H_{17}ClO_4$
7l	*m*-ClC_6H_4	CH_2Cl_2-SSB	140-141.5	79	$C_{15}H_{17}ClO_4$
7n	*p*-BrC_6H_4	CH_2Cl_2-SSB	176-178	92	$C_{15}H_{17}BrO_4$[b]
7o	3,4-$(Cl)_2C_6H_3$	Et_2O-PE	119-121.5	80	$C_{15}H_{16}Cl_2O_4$
7p	2,4-$(Cl)_2C_6H_3$	EtOAc	192-195.5	71	$C_{15}H_{16}Cl_2O_4$
7q	*p*-$[(CH_3)_3C]C_6H_4$	CH_2Cl_2-SSB	198-200	74	$C_{19}H_{26}O_4$

[a] Could not be satisfactorily recrystallized. [b] C: calcd, 52.80; found, 53.40.

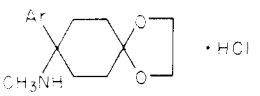
Table VII. 4-Aryl-4-isocyanatocyclohexanone Ethylene Ketals



no.	Ar	chromatogr solvent	rxn solvent	mp, °C	yield, %	formula
8a	C_6H_5	7.5EtOAc-SSB	PE	48-50	75	$C_{15}H_{17}NO_3$
8c	1-naphthyl	2EtOAc-CH_2Cl_2	Et_2O-SSB	111-114	60	$C_{19}H_{19}NO_3$
8d	*o*-$CH_3C_6H_4$	2EtOAc-CH_2Cl_2	*a*		80	
8e	*m*-$CH_3C_6H_4$	CH_2Cl_2	*a*		90	
8f	*p*-$CH_3C_6H_4$	0.10EtOAc-SSB	*a*		84	
8g	*m*-$(CH_3O)C_6H_4$	1.5EtOAc-CH_2Cl_2	*a*		25	
8h	*p*-$(CH_3O)C_6H_4$	2.5EtOAc-CH_2Cl_2	SSB	70.5-72	62	$C_{16}H_{19}NO_4$
8i	3,4-$(CH_3O)_2C_6H_5$	30EtOAc-SSB	*a*		28	
8j	*p*-FC_6H_4	1EtOAc-CH_2Cl_2	*a*		35	
8k	*o*-ClC_6H_4	10EtOAc-SSB	*a*		84	
8l	*m*-ClC_6H_4	CH_2Cl_2	*a*		97	
8m	*p*-ClC_6H_4	10EtOAc-SSB	PE	76.5-80	43	$C_{15}H_{16}ClNO_3$
8n	*p*-BrC_6H_4	CH_2Cl_2	Et_2O-PE	87-89	49	$C_{15}H_{16}BrNO_3$
8o	3,4-$(Cl)_2C_6H_3$	2.5EtOAc-CH_2Cl_2	*a*		71	
8p	2,4-$(Cl)_2C_6H_3$	1.5EtOAc-CH_2Cl_2	Et_2O-PE	85-89.5	77	$C_{15}H_{15}Cl_2NO_3$
8q	*p*-$[(CH_3)_3C]C_6H_4$	2EtOAc-CH_2Cl_2	SSB	103-105.5	71	$C_{19}H_{25}NO_3$

[a] Oily product, characterized by IR only (ν_{max} 2250-2270 cm^{-1}).

Table VIII. 4-Aryl-4-(methylamino)cyclohexanone Ethylene Ketals

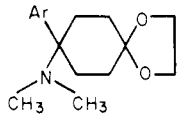


no.	Ar	salt	mp, °C	yield, %	formula
9a	C_6H_5	HCl	243-245	78	$C_{15}H_{22}ClNO_2$
9b	2-thienyl	HCl	211-214	35	$C_{13}H_{20}ClNO_2S$
9c	1-naphthyl		120-123.5	54	$C_{19}H_{23}NO_2$
9d	*o*-$CH_3C_6H_4$	HCl	231-233	60	$C_{16}H_{24}ClNO_2 \cdot 0.5H_2O$
9e	*m*-$CH_3C_6H_4$	HCl	219-221	58	$C_{16}H_{24}ClNO_2$
9f	*p*-$CH_3C_6H_4$		56-60	57	$C_{16}H_{23}NO_2$
9g	*m*-$(CH_3O)C_6H_4$	HCl	238-239	71	$C_{16}H_{24}ClNO_3$[c]
9h	*p*-$(CH_3O)C_6H_4$	*p*-TSA	206-208	88	$C_{23}H_{31}NO_6S$
9i	3,4-$(CH_3O)_2C_6H_3$	HI	200-201	57	$C_{17}H_{26}INO_4$
9j	*p*-FC_6H_4	HCl	262-263	56	$C_{15}H_{21}ClFNO_2$
9k	*o*-ClC_6H_4		*b*	96	
9l	*m*-ClC_6H_4	HCl	252-254	56	$C_{15}H_{21}Cl_2NO_2$
9m	*p*-ClC_6H_4		63.5-66.5	91	$C_{15}H_{20}ClNO_2$
9n	*p*-BrC_6H_4	HCl	266-267	69	$C_{15}H_{21}BrClNO_2$
9o	3,4-$(Cl)_2C_6H_3$	HCl	225-227	46	$C_{15}H_{20}Cl_3NO_2$
9p	2,4-$(Cl)_2C_6H_3$	HCl	201-203.5	68	$C_{15}H_{20}Cl_3NO_2 \cdot 0.33H_2O$
9q	*p*-$[(CH_3)_3C]C_6H_4$		118.5-121	94	$C_{19}H_{29}NO_2$

[a] Free base. [b] Amorphous as free base or salt. [c] C: calcd, 61.23; found, 60.07.

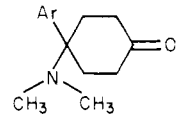
(Table IX). A solution of 0.013 mol of 4-aryl-4-(methylamino)cyclohexanone ethylene ketal (free base) and 18 mL of 37% formalin in 54 mL of methanol was heated at reflux for 4 h. The mixture was then cooled in ice and treated cautiously with 2.86 g of sodium borohydride over 10–15 min. The mixture was stirred at room temperature for 2 h, and the bulk of the solvent was then removed under vacuum. The residue was partitioned between water and methylene chloride. The organic layer was washed with

Table IX. 4-Aryl-4-(dimethylamino)cyclohexanone Ethylene Ketals



no.	Ar	salt	mp, °C	yield, %	formula
10a	C_6H_5	HCl	226-229	68	$C_{16}H_{24}ClNO_2$
10b	2-thienyl		99-103	18	$C_{14}H_{21}NO_2S$
10c	1-naphthyl		128-132	40	$C_{20}H_{25}NO_2$
10d	o-$CH_3C_6H_4$	HI	182-183.5	37	$C_{17}H_{26}INO_2 \cdot 0.5H_2O$
10e	m-$CH_3C_6H_4$	HI	214-215.5	85	$C_{17}H_{26}INO_2$
10f	p-$CH_3C_6H_4$	HCl	228-229	76	$C_{17}H_{26}ClNO_2$
10g	m-$(CH_3O)C_6H_4$	HCl	184-185.5	68	$C_{17}H_{26}ClNO_3$
10h	p-$(CH_3O)C_6H_4$	HCl	203-204	78	$C_{17}H_{26}ClNO_3$
10i	3-$(OCH_3)_2C_6H_3$		95-98.5	72	$C_{18}H_{27}NO_4$
10j	p-FC_6H_4		79.5-82	85	$C_{16}H_{22}FNO_2$
10k	o-ClC_6H_4	HI	208-213	12.6	$C_{16}H_{23}ClINO_2$
10l	m-ClC_6H_4	HCl	224-227	52	$C_{16}H_{23}Cl_2NO_2$
10m	p-ClC_6H_4	HCl	261-262	59	$C_{16}H_{23}Cl_2NO_2$
10n	p-BrC_6H_4	HCl	254-255.5	51	$C_{16}H_{23}BrClNO_2$
10o	3,4-$(Cl)_2C_6H_3$		77-81	51	$C_{16}H_{21}Cl_2NO_2$
10p	2,4-$(Cl)_2C_6H_3$	HCl	229.5-232	40	$C_{16}H_{22}Cl_3NO_2 \cdot 0.5H_2O$
10q	p-$[(CH_3)_3C]C_6H_4$		103.5-107	90	$C_{20}H_{31}NO_2$

Table X. 4-Aryl-4-(dimethylamino)cyclohexanones



no.	Ar	rxn solvent	mp, °C	yield, %	formula
11a	C_6H_5	Et_2O	98-99.5	69	$C_{14}H_{19}NO$
11b	2-thienyl	MeOH-H_2O	102-103	64	$C_{12}H_{17}NOS$
11c	1-naphthyl	CH_2Cl_2-SSB	149-151.5	25	$C_{18}H_{21}NO \cdot 0.25H_2O$
11d	o-$CH_3C_6H_4$[a]	MeOH-Et_2O	162-165	36	$C_{15}H_{22}INO$
11e	m-$CH_3C_6H_4$[a]	CH_2Cl_2-EtOAc	172-174.5	75	$C_{15}H_{22}INO$
11f	p-$CH_3C_6H_4$	PE	65-67.5	55	$C_{15}H_{21}NO$
11g	m-$(CH_3O)C_6H_4$	PE	57-59	45	$C_{15}H_{21}NO_2$
11h	p-$(CH_3O)C_6H_4$	SSB	89-91	66	$C_{15}H_{21}NO_2$
11i	3,4-$(OCH_3)_2C_6H_3$	Et_2O	97-98.5	71	$C_{16}H_{23}NO_3$
11j	p-FC_6H_4	Et_2O	126-128	75	$C_{14}H_{18}FNO$
11k	o-ClC_6H_4	Et_2O	81-84	26	$C_{14}H_{18}ClNO$
11l	m-ClC_6H_4	Et_2O-PE	93-95	81	$C_{14}H_{18}ClNO$[a]
11m	p-ClC_6H_4	Et_2O	108-111	70	$C_{14}H_{18}ClNO$
11n	p-BrC_6H_4	Me_2CO-SSB	115-118	69	$C_{14}H_{18}BrNO$
11o	3,4-$(Cl)_2C_6H_3$	Et_2O-PE	88.5-91	72	$C_{14}H_{17}Cl_2NO$
11p	2,4-$(Cl)_2C_6H_3$	Et_2O	116.5-120	68	$C_{14}H_{17}Cl_2NO$
11q	p-$[(CH_3)_3C]C_6H_4$	PE	82.5-87	60	$C_{18}H_{27}NO$

[a] C: calcd, 66.79; found, 67.39.

brine and taken to dryness. The residual gum was recycled through the above reaction conditions and workup. The crude product was dissolved in ether and treated with just sufficient ethereal hydrogen chloride. The precipitated salt was recrystallized from methylene chloride–ethyl acetate. When the free base was a solid, this was recrystallized as such.

4-Aryl-4-(dimethylamino)cyclohexanones (Table X). A solution of 4 mmol of 4-aryl-4-(dimethylamino)cyclohexane ethylene ketal or its salt in 7 mL of 2.5 N hydrochloric acid and 14 mL of methanol was allowed to stand at room temperature for 48 h. The bulk of the solvent was then removed under vacuum and the residue made strongly basic with 50% sodium hydroxide. The precipitate was extracted with ether. The organic layer was washed with water and brine and taken to dryness. The residue, if solid, was recrystallized; if not, the compound was first converted to a hydrohalide salt and recrystallized in this form.

***N,N*-Dimethyl-1-phenylcyclohexyl-1-amine (13).** To a solution of 15.2 g (0.10 mol) of *N,N*-dimethyl-1-(cyanophenyl)-cyclohexyl-1-amine in 100 mL of THF there was added 50 mL (0.14 mol) of 2.85 M phenylmagnesium bromide in ether. Following 18 h of standing at room temperature, the mixture was cooled in ice and treated with 75 mL of saturated ammonium chloride and 25 mL of water. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was dissolved in ether, and this solution was extracted with 5 portions of 25 mL each 2.5 N hydrochloric acid. The acid extracts were allowed to stand at room temperature for 18 h, extracted with ether, and made strongly basic. The precipitated oil was taken up in ether and this last solution treated with 1 N ethereal hydrogen chloride. The solid which separated was recrystallized several times from methylene chloride–ethyl acetate to give 7.88 g (33%) of product, mp 164–165 °C, whose NMR spectrum is in consonance with the structure. M_r calcd 203 (free base); MS m/e 203. No satisfactory analysis could be obtained. Anal. Calcd for $C_{14}H_{22}ClN \cdot 0.5\ CH_2Cl_2$: C, 61.70; H, 8.21; N, 4.99; M_r (free base) 203. Found: C, 62.69; H, 8.59; N, 5.08; MS (M^+) m/e 203.

4-Carbethoxy-4-cyclopentylcyclohexanone Ethylene Ketal (15). To an ice-cooled solution of 10.0 g (0.10 mol) of diisopropylamine in 100 mL of THF under nitrogen there was added 62 mL of 1.68 N butyllithium in pentane. There were then added dropwise, in sequence, 21.4 g (0.10 mol) of 4-carbethoxycyclopentanone in 100 mL of THF and a solution of 14.9 g (0.10 mol) of cyclopentyl bromide and 17.9 g (0.10 mol) of hexamethylphosphoramide in 50 mL of THF. The mixture was stirred for 3 h in the cold and 18 h at room temperature. The solution was again cooled in ice and treated with 75 mL of saturated aqueous

ammonium chloride and 25 mL of water and benzene. The organic layer was washed with water and brine and taken to dryness. The residual oil was distilled at 0.2 mm to give 2.37 g (88%) of product, bp 116–124 °C. Anal. ($C_{16}H_{26}O_4$) C, H.

4-Carboxy-4-cyclopentylcyclohexanone Ethylene Ketal (16). A mixture of 10.0 g (0.035 mol) of the ester and 2.10 g of NaOH in 80 mL of ethylene glycol was heated at reflux for 18 h. The mixture was worked up exactly as above and the product recrystallized (SSB) to give 7.22 g (51%) of acid, mp 110–113 °C. Anal. ($C_{14}H_{22}O_4$) C, H.

4-Cyclopentyl-4-(methylamino)cyclohexanone Ethylene Acetal Hydrochloride (18). The acid (16) obtained above was rearranged to the isocyanate exactly as above [7.81 g, $(C_6H_5O)_2POH_3$; 3.95 mL of THF]. The isocyanate (oil, ν_{max} 2280) obtained on chromatography was reduced by means of $LiAlH_4$ (1.0 g). The basic product obtained after the usual workup was recrystallized as the HCl salt to give 2.50 g (32%) of crystals, mp 179–182 °C. Anal. ($C_{14}H_{26}ClNO_2$) C, H, N.

4-Cyclopentyl-4-(dimethylamino)cyclohexanone Ethylene Ketal Hydrochloride (19). The free base from the above secondary amine hydrochloride was subjected to the standard methylation procedure (CH_2O, $NaBH_4$) twice. The product was recrystallized (CH_2Cl_2–EtOAc) as the HCl salt to give 0.62 g (24%) of salt, mp 200–203 °C. Anal. ($C_{15}H_{28}ClNO_2$) C, H, N.

4-Cyclopentyl-4-(dimethylamino))cyclohexanone Hydrochloride (20). Hydrolysis of 1.14 g of the acetal as above afforded on crystallization (CH_2Cl_2–EtOAc) 0.63 g (66%) of the ketone, hydrochloride salt. Anal. ($C_{13}H_{24}ClNO$) C, H, N.

Biology. Methods. The biological testing consisted of a battery of standard assays.[8] Briefly, CF-1 female mice were dosed sc with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch, and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[10]

(10) D. J. Finney, "Statistical Method in Biological Assay", Hafner Publishing Co., New York, 1952.

Synthesis and Structure-Activity Studies of a Series of 7α-Halogeno Corticosteroids[1]

Ho-Jane Shue, Michael J. Green,*

Department of Natural Products Research

Joseph Berkenkoph, Margaret Monahan, Xiomara Fernandez, and Barry N. Lutsky*

Department of Physiology, Schering-Plough Research, Schering-Plough Corporation, Bloomfield, New Jersey 07003.
Received June 7, 1979

The preparation and topical antiinflammatory potencies of a series of 7α-halogeno-16-substituted-prednisolone derivatives are described. The 7α-chloro, 7α-bromo, and 7α-iodo corticosteroids were obtained by addition of hydrogen halide to the 6,7-dehydro compounds. The extent of addition of HCl varied with substitution at C-11, while no addition of HF was observed at all. The 7α-fluoro corticosteroids were prepared by reaction of the appropriate 7β-hydroxy compounds with *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine. The 7β-hydroxy steroids were obtained, in turn, from the 6,7-dehydro compounds via the 6β,7β-dihydroxy derivatives. Antiinflammatory potencies were measured in mice by the Tonelli croton oil ear assay. The greatest effect of a 7α-halogen was observed in the 16α-methylprednisolone series, where 7α-chloro and 7α-bromo substitution increased potency 2.5- to 3.5-fold. Compounds **4b** and **5b** were equipotent to betamethasone dipropionate. 7α-Halogen substitution in other series produced more variable effects and sometimes led to a reduction of antiinflammatory potency.

Since the pioneering efforts of Sulzberger and co-workers in the dermatological use of topical hydrocortisone,[2,3] many chemical modifications of the natural hormones have been made in attempts to improve existing therapy. Most of the important structural changes have involved halogenation at C_6 and/or C_9,[4,5] methylation[6,7] or hydroxylation[8] at C_{16}, and introduction of a 1,2 double bond.[9] Furthermore, it was shown that topical activity could be enhanced

(1) Part of this material was presented in preliminary form at the 5th International Congress on Hormonal Steroids, New Delhi, India, Nov 1978, by M. J. Green, J. Berkenkoph, X. Fernandez, M. Monahan, H.-J. Shue, R. L. Tiberi, and B. N. Lutsky, abstract S. 1 (2); *J. Steroid Biochem.*, 11, 61 (1979).

(2) Trivial names employed are hydrocortisone (11β,17α,21-trihydroxy-4-pregnene-3,20-dione), betamethasone valerate (9α-fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-valerate), betamethasone dipropionate (9α-fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate).

(3) M. Sulzberger and V. H. Witten, *J. Invest. Dermatol.*, 19, 101 (1952); M. Sulzberger, V. H. Witten, and C. C. Smith, *J. Am. Med. Assoc.*, 151, 468 (1953).

(4) J. A. Fried, *Ann. N.Y. Acad. Sci.*, 61, 573 (1955).

(5) J. A. Hogg, G. B. Spero, J. L. Thompson, J. B. Magerlein, W. P. Schneider, D. H. Peterson, D. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind. (London)*, 1002 (1958).

(6) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, 80, 3160 (1958); G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, 80, 3161 (1958).

(7) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, 80, 4428 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *ibid.*, 80, 4435 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, 82, 4012 (1960).

(8) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, 78, 1909 (1956).

(9) S. Tolksdorf, M. L. Battin, J. W. Cassidy, R. M. McLeod, F. H. Warren, and P. L. Perlman, *Proc. Soc. Exp. Biol. Med.*, 92, 207 (1956).

0022-2623/80/1823-0430$01.00/0