Nalorphine-like Properties of Some 2,3-Dimethyl-3-arylpiperidines

Maria A. Iorio*

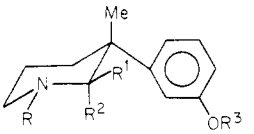
Laboratory of Pharmaceutical Chemistry, Istituto Superiore di Sanità, 00161 Rome, Italy

and Alan F. Casy

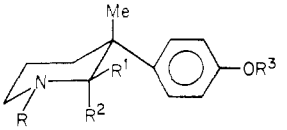
Pharmacy Department, Norfolk and Norwich Hospital, Norwich NR1 3SR, United Kingdom. *Received October 21, 1977*

A number of N-substituted 2,3-dimethyl-3-arylpiperidines having an *m*- or *p*-arylhydroxyl were prepared and evaluated for analgesic agonist and antagonist properties. The diastereomeric *N*-allyl and *N*-cyclopropylmethyl derivatives behaved as pure potent antagonists. Substitution of the arylhydroxyl from the meta to the para position resulted in a net fall of the antagonist activity.

Previously we confirmed and extended[1] the report of Kugita et al.[2] that certain derivatives of 2,3-dimethyl-3-arylpiperidine possess morphine-like or nalorphine-like properties. In continuation of this work the synthesis and



α-1, R^1 = H; R^2 = Me; R^3 = Me
β-1, R^1 = Me; R^2 = H; R^3 = Me
α-2, R^1 = H; R^2 = Me; R^3 = H
β-2, R^1 = Me; R^2 = H; R^3 = H



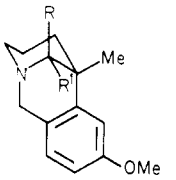
α-3, R^1 = H; R^2 = Me; R^3 = Me
β-3, R^1 = Me; R^2 = H; R^3 = Me
α-4, R^1 = H; R^2 = Me; R^3 = H
β-4, R^1 = Me; R^2 = H; R^3 = H

a, R = H; b, R = Me; c, R = CH_2CH_2Ph; d, R = $CH_2CH{=}CH_2$; e, R = CH_2-c-C_3H_5; f, R = $CH_2CH{=}CMe_2$; g, R = COMe

pharmacology of the derivatives α- and β-**2e,f** and α-**4d–f** are now reported; of these, one diastereomeric form of **2e** has been examined pharmacologically but its stereochemistry not characterized.[3] Points of interest in the synthetic work, which chiefly followed methods already described,[4] are outlined below (Scheme I).

Compound **5** was obtained by base-catalyzed methylation of *p*-methoxyphenylacetone.[5] Reaction of **5** with acrylonitrile gave the acyclic intermediate **6** and the latter was converted to the cyclic imine **7** by catalytic hydrogenation over Raney nickel. Reduction of **7** with H_2–Pd/C, $LiAlH_4$, or $NaBH_4$ gave a diastereomeric mixture of **3a** in which the α isomer preponderated over the β form forming about 85% of the mixture; in contrast, reduction of **8** with H_2–Pd/C furnished similar amounts of the two isomers of 1a.[4] Attempts to O-demethylate the 1-cyclopropylmethyl and 1-(3,3-dimethyl)allyl derivatives α- and β-**1e,f** and α-**3e,f** using 48% HBr at reflux temperature led to transformation of the 1-substituent, but reaction with BBr_3 at −60 °C proved successful.[6] N-Methylation of α- or β-**3a** under Eschweiler–Clarke conditions proceeded normally to give α- or β-**3b**; similar treatment of α- or β-1a gave α- or β-**9**[7] due to the activating influence of the methoxy substituent.

The *cis*-2-Me,3-Ar and *trans*-2-Me,3-Ar stereochemistries were assigned to α- and β-racemates of **3** on the basis of ^1H NMR chemical shift comparisons and relationships with spectra of α- and β-1 of known stereochemistry[4] (Table I). Data obtained support piperidine chair conformations with axial 2-Me in the α and equatorial 2-Me



α-9, R^1 = Me; R^2 = H
β-9, R^1 = H; R^2 = Me

in the β series with the orientations of the C-3 substituents being unchanged.

Differences in the spectra of the *N*-acetyl diastereomers **3g** are quite significant and are used as evidence of the stereochemistry of the α and β series. In α-**3g** there is a duplication of 2-Me, 3-Me, and amide methyl signals because the axial 2-Me group does not hinder either of the rotamers (a and b) which arise as a result of slow rotation about amide N–C bond (Chart I).[8] The magnetic environments of 2-Me, 3-Me, and amide methyl groups in a and b differ sufficiently to allow the observation of separate signals of equal intensity. In β-**3g** only one signal for the above-mentioned groups is apparent. In this case rotamer c is hindered by steric repulsion of equatorial 2-Me and amide methyl; hence, only rotamer d is significantly populated. Furthermore, the 2-Me resonance of the β isomer moves to a low-field position as it falls under the deshielding influence of the amide carbonyl.

Replacement of N–H by N–Me (α- and β-**3a** → α- and β-**3b**) causes an upfield shift of 0.78 ppm for the 2-H of the β form and of 0.21 ppm for the 2-H of the α form. This effect is in agreement with β-2-H being axial since equatorial Me (in this case N–Me equatorially orientated) shields an adjacent axial H more than an equatorial H.[9] Furthermore, except for the α/β pair **3a** (R = H), the β-2-H is always higher field than the α-2-H and this shielding is attributed to the trans-diaxial orientation of the nitrogen lone pair and β-2-H.[1,10]

Pharmacologic Evaluation. The derivatives with an *m*-phenolic group (α- and β-**2e,f**) and those with a *p*-phenolic group of the α series (α-**4b–f**) (insufficient amounts of the β series were available for pharmacologic testing) were screened for morphine-like and nalorphine-like properties. In the hot-plate test[11,12] (white male mice, sc administration as hydrochloride salts in aqueous solution) α-**4b** and α-**4c** (R = Me and phenethyl) did not show analgesic activity up to a dose level of 100 mg/kg; in contrast, α-**2c** in the corresponding *m*-phenolic series was found active[1,2] with an ED_{50} less than 10 mg/kg. In the *m*-phenolic series α- and β-**2e,f** were inactive as analgesics in the Nilsen test[13] up to a dose level of 20 mg/kg, in agreement with previous findings for the 1-allyl pair **2d**.[1-3]

All the compounds bearing an allyl, cyclopropylmethyl, or dimethylallyl substituent on nitrogen were tested for antagonist properties by the fentanyl antagonism test in

0022-2623/78/1821-0812$01.00/0

Scheme I

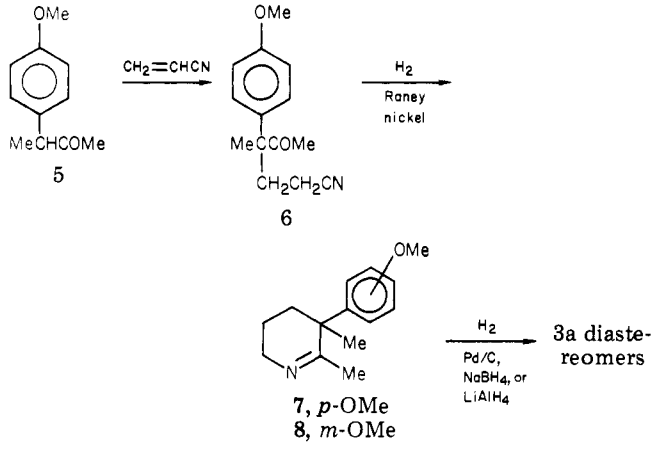


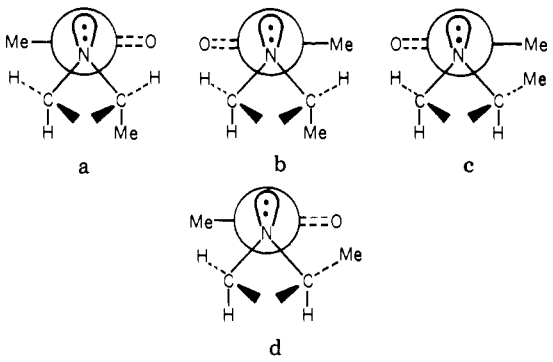
Table I. ^{1}H NMR Spectral Data[a] of Some 2,3-Dimethyl-3-(*p*-methoxyphenyl)piperidines

Compd	2-*sec*-Me (d)	3-*t*-Me (s)	2-H (q)	N-R
α-3a	0.95	1.35	2.93	2.20 (s)
α-1a[b]	0.94	1.36	2.96	1.76 (s)
β-3a	0.78	1.36	3.15	3.00 (s)
β-1a[b]	0.74	1.34	3.11	1.81 (s)
α-3b	0.65	1.42	2.72	2.30 (s)
α-1b[b]	0.64	1.41	2.75	2.30 (s)
β-3b	0.77	1.38	2.37	2.27 (s)
β-1b[b]	0.75	1.39	2.35	2.25 (s)
α-3c	0.56	1.41	3.00	2.72[c]
α-1c[b]	0.57	1.41	3.03	2.73[c]
β-3c	0.82	1.33	2.87	2.80[c]
β-1c[b]	0.81	1.33	2.89	2.76[c]
α-**3g**	0.75, 0.86	1.29, 1.37		2.17 (s), 2.21 (s)
α-1g[b]	0.75, 0.86	1.30, 1.35		2.15 (s), 2.20 (s)
β-**3g**	1.31	1.10		1.97 (s)
β-1g[b]	1.27	1.12		2.00 (s)

[a] Chemical shifts in ppm (δ) from internal Me_4Si as 10% solutions in $CDCl_3$ at 60 MHz; d = doublet (J = 6-7 Hz), s = singlet, q = quartet (J = 6-7 Hz). [b] Reference 4. [c] Main peak of multiplet for N-CH_2CH_2 protons.

rats (tests carried out by Dr. K. Schellekens of Janssen Pharmaceutica, Beerse, Belgium). In this procedure fentanyl is injected subcutaneously in rats at the very high standard dose of 0.63 mg/kg which results in pronounced respiratory depression, loss of righting reflex, lead pipe rigidity, and analgesia. The test compound was then given intravenously as hydrochloride salts in aqueous solution (each dose level in a minimum of three rats) and the dose needed to reverse the effects of fentanyl determined. Effective doses in milligrams per kilogram together with those of the standard antagonist, nalorphine, are given in Table II.

Chart I. Rotational Conformers of α-**3g** (a and b) and β-**3g** (c and d) about the Amide N-C Bond

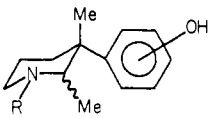


Results and Discussion

Inspection of Table II reveals that both the substitution on nitrogen and the molecular stereochemistry have an important influence upon antagonist activity. The cyclopropylmethyl substituent endowed compounds α- and β-**2e** with potent antagonist properties equal to or greater than those of nalorphine and the corresponding *N*-allyl analogues α- and β-**2d**,[1-3] while the *N*-(2,3-dimethyl)allyl substituent yielded less potent antagonists, α- and β-**2f**. Of the diastereomeric pairs **2e** and **2f**, the β isomer was the more potent (twice the potency or greater), in agreement with previous finding for the *N*-allyl isomers **2d** (β-**2d** is twice as active as nalorphine and four times as active as α-**2d** in antagonizing fentanyl-induced effects).[1]

Movement of the phenolic function from the meta to the para position of the aryl ring resulted in a sharp drop in potency in all three cases (α-**2d**/**4d**, α-**2e**/**4e**, and α-**2f**/**4f**); these results emphasize the importance of an *m*-hydroxyaryl moiety for ligands that bind to opiate receptors. Among the antagonists α-**4d**–**f**, the *N*-(3,3-dimethyl)allyl member again proved the least potent.

Table II. Antagonist Properties of Some 2,3-Dimethyl-3-(*m*- or *p*-hydroxyphenyl)piperidines vs. Fentanyl Effects



Compd	R	OH	Antagonism vs. fentanyl effects; active dose,[a] mg/kg iv in rats: Respiration	Righting reflex	Rigidity score	Analgesia (<10 s)[b]	Duration of action, min
α-**2e**[c]	CH_2-c-C_3H_5	Meta	0.16	1.25	0.31	1.25	<30 at 1.25
β-**2e**	CH_2-c-C_3H_5	Meta	0.08	0.31	0.16	0.63	≤60 at 0.63
α-**2f**	$CH_2CH=C(Me)_2$	Meta	1.25-2.5	≥2.5	2.5	2.5	<30 at 2.5
β-**2f**	$CH_2CH=C(Me)_2$	Meta	0.31-0.63	>2.5	1.25	2.5	<30 at 2.5
α-**4d**	$CH_2CH=CH_2$	Para	1.25	>2.5	1.25-2.5	2.5	<30 at 2.5
α-**4e**	CH_2-c-C_3H_5	Para	0.63	≥2.5	1.25	≥2.5	
α-**4f**	$CH_2CH=C(Me)_2$	Para	2.5	*d*	≥2.5	*d*	
Nalorphine			0.16-0.31	1.25-2.5	0.63	0.63-1.25	Short[b]

[a] The active dose represents the one that abolishes the above listed effects of fentanyl given at the standard dose of 0.63 mg/kg sc in rats; these active doses are significant at the level of $p < 0.001$ (Fisher exact probability test). [b] This is measured in the tail withdrawal reflex test and it means the restoration of the reaction time of the treated animal to the control level (<6 s): P. A. J. Janssen, C. J. E. Niemegeers, and J. C. H. Dony, *Arzneim.-Forsch.*, 13, 502 (1963). [c] The uncharacterized derivative **2e** (ref 3) was reported to be devoid of analgesic properties and one-fifth and one-half as active as nalorphine in antagonizing analgesia in mice and respiratory depression in rabbits, respectively. [d] Inactive at 2.5 mg/kg.

Similar potency comparisons were found for *N*-allyl, *N*-cyclopropylmethyl, and *N*-(3,3-dimethyl)allyl derivatives in the morphinans and 6,7-benzomorphans with antagonist properties.[14,15]

The more active isomeric pair **2e** was tested in morphine-dependent monkeys. In the single dose suppression test (SDS)[16] α-**2e** precipitated immediate, severe, short-lasting abstinence signs at 1 mg/kg and in nonwithdrawn morphine-dependent monkeys precipitated the withdrawal syndrome (0.5–2 mg/kg) with a fast onset, short-lasting effect comparable to nalorphine.[17] In the SDS test β-**2e** did not substitute for morphine and may have exacerbated withdrawal (myoclonic jerks were seen at 0.5–1.0 mg/kg) and precipitated abstinence signs in nonwithdrawn morphine-dependent monkeys (1.0–3.0 mg/kg).[18] These findings are in fair agreement with those previously obtained for the *N*-allyl pair **2d** (α-**2d** and β-**2d** precipitated dose-related withdrawal with fast onset and short duration of action at 0.5–4.5 and 0.05–0.5 mg/kg, respectively)[18,19] and confirm that both pairs **2d** and **2e** act as potent antagonists which lack agonistic activity as shown in the Nilsen test.

The results of the present investigation demonstrate that potent antagonists can be found in relatively simple molecules such as 3-arylpiperidines, providing that they possess an aryl hydroxyl in the meta position and a proper substituent on nitrogen.

Experimental Section

Melting points (uncorrected) were taken on a Büchi-Tottoli capillary apparatus. The ^{1}H NMR spectra were recorded at 60 MHz with a Varian T-60 spectrometer as 10% solutions in $CDCl_3$ (Me_4Si internal standard). Microanalyses were performed by the Microanalytical Department (ISS) under the direction of Dr. A. Mazzeo-Farina and are within 0.4% of the calculated values.

3-(*p*-Methoxyphenyl)-2-butanone (5). To a stirred suspension of $NaNH_2$ (prepared from Na, 10 g) in 400 mL of dry Et_2O was added dropwise *p*-methoxyphenylacetone (68 g, 0.41 mol) at 10 °C. After 2 h of stirring at room temperature, CH_3I (37 mL, 0.60 mol) in 100 mL of Et_2O was added dropwise at 10 °C. After refluxing for 2 h, the cooled mixture was poured into ice; the Et_2O layer was separated, dried (Na_2SO_4) and evaporated. Distillation of the residue gave 24 g (33%) of **5** as a pale yellow oil: bp 65–67 °C (0.2 mm); NMR (CCl_4) δ 1.26 (d, *sec*-CH_3), 1.32 (s, $COCH_3$), 3.67 (q, CH). The semicarbazone melted at 183–184 °C from EtOH. Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

5-Cyano-3-(*p*-methoxyphenyl)-3-methyl-2-pentanone (6). To a stirred solution of **5** (36 g, 0.19 mol) in 100 mL of dry dioxane was added 4.5 g of Triton B and then 14 g of acrylonitrile in 30 mL of dioxane at a rate to maintain the internal temperature at 35–40 °C. After refluxing for 30 min, the solution was concentrated, diluted with H_2O, and extracted with Et_2O. Drying (Na_2SO_4) and evaporation gave an oily residue. The fraction collected at 120–125 °C (0.02 mm) gave 23.7 g (51%) of **6**: n^{21}_D 1.5353; NMR (CCl_4) δ 1.54 (s, CH_3), 1.87 (s, $COCH_3$), 2.09 (apparent s, CH_2CH_2CN). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

2,3-Dimethyl-3-(*p*-methoxyphenyl)-3,4,5,6-tetrahydropyridine (7). Hydrogenation of **6** (20 g in 150 mL of 95% EtOH) over Raney nickel at 4 atm and 65 °C gave 17 g of **7** together with a small amount of **3a**. The analytical sample was purified by chromatography (alumina, III, Et_2O): bp 94–96 °C (0.5 mm); n^{20}_D 1.5525. Anal. ($C_{14}H_{19}NO$) C, H, N.

Isomeric 2,3-Dimethyl-3-(*p*-methoxyphenyl)piperidines (3a). To a stirred solution of **7** (21.7 g, 0.1 mol) in 200 mL of MeOH, $NaBH_4$ (7.6 g, 0.2 mol) was added over 30 min at 15–20 °C. After stirring at room temperature for 3 h, the mixture was evaporated and the residue distributed between H_2O and Et_2O. The Et_2O extract was dried (Na_2SO_4) and evaporated to give 16.6 g (70%) of a crude mixture of α- and β-**3a**. The mixture was treated with ethanolic HCl and diluted with Et_2O. The solid which separated after two crystallizations from EtOH gave pure α-**3a**·HCl. The residue from the mother liquors (as free base) was chromatographed on alumina (III, neutral) using Et_2O with increasing concentration of MeOH from 1 to 5% as the elution system. Column effluent fractions were checked by TLC [Al_2O_3 G Merck, Et_2O–MeOH (9:1)] and spots detected by spraying with Dragendorff's reagent. The β-**3a** isomer was the faster running component (β, R_f 0.59; α, R_f 0.47).[20] The separated bases were characterized as hydrochlorides (Table III). The approximate α/β ratio of the total mixture was 6:1.

Table III. N-Substituted 2,3-Dimethyl-3-arylpiperidines

Compd	Mp, °C	Crystn solvent[a]	Formula[b]
α-**1e**·HCl	221–222	E	$C_{18}H_{28}ClNO$
β-**1e**·HCl	187–188	E-A-ET	$C_{18}H_{28}ClNO$
α-**2e**·HCl	240–241	E-ET	$C_{17}H_{26}ClNO$
β-**2e**·HCl	238–239	E-ET	$C_{17}H_{26}ClNO$
α-**1f**·HCl	201–202	E-ET	$C_{19}H_{30}ClNO$
β-**1f**·HCl	195–196	E-ET	$C_{19}H_{30}ClNO$
α-**2f**·HCl	205–206	E-ET	$C_{18}H_{28}ClNO$
β-**2f**·HCl	239–240	E-ET	$C_{18}H_{28}ClNO$
α-**3a**·HCl	217–218	E-ET	$C_{14}H_{22}ClNO$
β-**3a**·HCl	272–273	E-ET	$C_{14}H_{22}ClNO$
α-**3b**·HCl	187–188	E-ET	$C_{15}H_{24}ClNO$
β-**3b**·HCl	250–251	E-ET	$C_{15}H_{24}ClNO$
α-**4b**	133–134	ET-PE	$C_{14}H_{21}NO$
α-**4b**·HBr	160–162	E	$C_{14}H_{22}BrNO$
α-**3c**·$(COOH)_2$	214–215	95% E	$C_{24}H_{31}NO_5$
β-**3c**·HCl	205–206	E-ET	$C_{22}H_{30}ClNO$
α-**4c**	150–151	ET-H	$C_{21}H_{27}NO$
α-**4c**·HCl	236–237	E-ET	$C_{21}H_{28}ClNO$
α-**3d**·HCl	210–211	E-ET	$C_{17}H_{26}ClNO$
α-**4d**·HCl	223–224	E-ET	$C_{16}H_{24}ClNO$
α-**3e**·HCl	209–210	E-ET	$C_{15}H_{25}ClNO$
α-**4e**·HCl	272–274	E	$C_{17}H_{26}ClNO$
α-**4e**·HBr	264–265	95% E	$C_{17}H_{26}BrNO$
α-**3f**·HCl	209–210	E-ET	$C_{19}H_{30}ClNO$
β-**3f**·HCl	230–231	E-ET	$C_{19}H_{30}ClNO$
α-**4f**·HCl	231–232	E-ET	$C_{18}H_{28}ClNO$
α-**4f**·HBr	247–248	E	$C_{18}H_{28}BrNO$
α-**3g**	59–62	ET-H	$C_{16}H_{23}NO_2$
β-**3g**	*c*		$C_{16}H_{23}NO_2$

[a] E, EtOH; A, Me_2CO; ET, Et_2O; H, hexane; PE, petroleum ether (bp 30–50 °C). [b] All compounds provided satisfactory analyses for C, H, and N. [c] This compound was an oil, bp 140–145 °C (0.05 mm) (short path).

***N*-Methyl Derivatives α- and β-3b.** A mixture of 1 g (ca. 5 mmol) of α-**3a**, 3 mL of HCOOH, and 2.4 mL of 40% of HCHO was refluxed for 6 h. The mixture was made alkaline with 20% NaOH and extracted with Et_2O. The ethereal extract was dried (Na_2SO_4) and evaporated and the oily residue was distilled in a ball tube oven [bp 95–105 °C (0.3 mm)] to give 0.90 g (85%) of α-**3b** which was converted to the hydrochloride. β-**3b** was prepared in a similar manner and yield from 100 mg of β-**3a** (Table III).

***N*-Phenethyl Derivatives α- and β-3c.** A mixture of 2.19 g (10 mmol) of α-**3a**, 2.10 g (11.3 mmol) of 2-phenylethyl bromide, and 2 g of K_2CO_3 in 25 mL of EtOH was heated under reflux for 48 h. The solvent was evaporated under vacuum and the residue partitioned between H_2O and Et_2O. Evaporation of the solvent left a residue which was characterized as the oxalate (yield 82%). β-**3c** was prepared in a similar manner from 200 mg of β-**3a** and crystallized as the hydrochloride (Table III).

***N*-Allyl Derivative α-3d.** A mixture of 2.19 g (10 mmol) of α-**3a**, 1.1 mL (12.7 mmol) of allyl bromide, 2 g of K_2CO_3, and 25 mL of EtOH was refluxed for 48 h and evaporated to dryness in vacuo. The residue was partitioned between H_2O and Et_2O, and the ethereal extract was dried (Na_2SO_4) and evaporated to give 1.61 g (62%) of α-**3d** which was characterized as the hydrochloride (Table III).

***N*-Cyclopropylmethyl Derivatives α- and β-1e, α-3e.** To a solution of the corresponding secondary amine (2.5 g) in 10 mL of dry C_6H_6 and 2 mL of pyridine, 2 g of cyclopropylcarbonyl chloride was added. After standing overnight at room temperature, the mixture was partitioned between H_2O and C_6H_6. The organic layer was washed with 10% $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was dissolved in dry Et_2O and added dropwise to a stirred suspension of $LiAlH_4$ (2 g) in 50 mL of dry Et_2O cooled at 5 °C. After the addition, the mixture was refluxed

for 1 h, ice cooled, carefully decomposed with 4 mL of H_2O followed by 2 mL of 8% NaOH, and filtered from the inorganic salts. The Et_2O solution was dried (Na_2SO_4) and evaporated. The oily base was characterized as the hydrochloride (yield 85–90%) (Table III).

***N*-(3,3-Dimethyl)allyl Derivatives α- and β-1f, α- and β-3f.** A mixture of 2 g (ca. 10 mmol) of the corresponding secondary amine, 2.3 mL (20.4 mmol) of 1-chloro-2-methyl-2-butene, 2 g of K_2CO_3, and 25 mL of EtOH was refluxed for 4 days [TLC monitoring, Al_2O_3 G Merck, petroleum ether–Et_2O (2:1)] and evaporated to dryness in vacuo. The residue was distributed between H_2O and Et_2O. The ethereal extract was dried (Na_2SO_4) and evaporated. The oily residue was characterized as the hydrochloride (yield 80–85%) (Table III).

***N*-Acetyl Derivatives α- and β-3g.** A mixture of α-**3a** (400 mg, ca. 2 mmol) in 12 mL of dry C_6H_6, 0.3 mL of pyridine, and 0.6 mL of acetyl chloride was left overnight at room temperature. The excess of chloride was decomposed with water and the organic layer separated, washed with 10% $NaHCO_3$ and dried (Na_2SO_4). Evaporation under vacuum afforded an oil which slowly solidified. The solid was crystallized to yield white crystals (350 mg, 73%). β-**3g** was prepared similarly as a clear oil starting from 100 mg of β-**3a** (Table III).

***O*-Demethyl Derivatives α-4b, α-4c, and α-4d.** A solution of 2 g of the corresponding methoxyphenyl derivative in 10 mL of 48% HBr was refluxed for 1 h under nitrogen. The cooled solution was made alkaline with aqueous 10% $NaHCO_3$ and extracted with Et_2O or $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated, and the base was converted to the HCl or HBr salts (yields 55–60%) (Table III).

***O*-Demethyl Derivatives α- and β-2e, α- and β-2f, α-4e, and α-4f.** To a stirred solution of the corresponding methoxyphenyl derivative (2.5 g, 8–9 mmol) in 15 mL of CH_2Cl_2 cooled at −60 °C was added a solution of BBr_3 (1.90 mL, 20 mmol) in 10 mL of CH_2Cl_2 cooled at the same temperature. After stirring at −60 °C for 1 h and at room temperature for 30 min, the mixture was cooled again at −60 °C, the boron–ether complex decomposed with MeOH, and the solvent evaporated under vacuum. The crude gummy solid was triturated with Et_2O, the Et_2O decanted, and the solid dissolved in hot EtOH and allowed to cool, affording 1.7–1.8 g (ca. 55%) of pink crystals of the corresponding phenolic derivative as hydrobromide. The hydrobromide was dissolved in water, made alkaline with NH_4OH, extracted with Et_2O, and dried (Na_2SO_4). Evaporation afforded the oily base which was converted to the HCl or HBr salts (Table III).

Acknowledgment. We wish to thank the Committee on Problems of Drug Dependence, Inc., for their tests for narcotic antagonism in monkeys and Dr. K. Schellekens of Janssen Pharmaceutica for the antagonist tests in rats.

References and Notes

(1) M. A. Iorio and A. F. Casy, *J. Pharm. Pharmacol.*, **27**, 140 (1975).
(2) H. Kugita, T. Oine, H. Inoue, and G. Hayashi, *J. Med. Chem.*, **8**, 313 (1965). By these authors α-**2c** was found active as an analgesic (ED_{50} = 9.77 mg/kg sc in mice) and α-**2d** active as an antagonist against morphine analgesia in mice.
(3) S. Nurimoto and G. Hayashi, *Jpn. J. Pharmacol.*, **23**, 742 (1973). α-**2d** was found one-ninth as active as nalorphine in antagonizing morphine analgesia in mice and almost one-half as active as nalorphine in antagonizing morphine-induced respiratory depression in rabbits.
(4) A. F. Casy and M. A. Iorio, *Gazz. Chim. Ital.*, **104**, 655 (1974).
(5) R. V. Heinzelman, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 573.
(6) D. C. Bishop, J. F. Cavalla, I. M. Lokhart, M. Wright, C. V. Winder, A. Wong, and M. Stephens, *J. Med. Chem.*, 11, 466 (1968).
(7) M. A. Iorio and A. F. Casy, *Gazz. Chim. Ital.*, **104**, 1243 (1974).
(8) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Am. Chem. Soc.*, **89**, 5067 (1967).
(9) H. Booth, *Tetrahedron*, **22**, 615 (1966).
(10) A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry", Academic Press, London, 1971, p 162.
(11) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).
(12) A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965).
(13) T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, and E. L. May, *J. Pharm. Sci.*, **61**, 86 (1972).
(14) A. F. Casy in "Progress in Medicinal Chemistry", Vol. 7, G. P. Ellis and G. B. West, Ed., Appleton-Century-Crofts, New York, N.Y., 1970, p 229.
(15) A. E. Jacobson in "Handbook of Psychopharmacology", Vol. 12, L. L. Iversen, S. D. Iversen, and S. H. Snyder, Ed., Plenum Press, New York, N.Y., in press.
(16) Committee on Problems of Drug Dependence, *Bull. Narc.*, **25** (no. 2), 25 (1973).
(17) H. H. Swain, personal communication, University of Michigan.
(18) M. D. Aceto, personal communication, Medical College of Virginia.
(19) M. A. Iorio, A. F. Casy, E. L. May, and W. A. Klee in Proceedings of the Second Congress of the Ungarian Pharmacological Society, Budapest, 1974.
(20) After alkylation the higher R_f compound was the α isomer [Al_2O_3 G Merck, petroleum ether–Et_2O (1:1)]. Similar behavior was observed for the α/β pairs of the *m*-methoxy series.

Potential Antitumor Agents. Synthesis, Reactivity, and Cytotoxicity of α-Methylene Carbonyl Compounds

John M. Cassady,* S. R. Byrn,* I. K. Stamos, S. M. Evans, and A. McKenzie

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. *Received February 9, 1978*

The α-methylene lactones **9**, **12**, **21**, and **24** were prepared by a mild, convenient α-methylenation process using the α-ethyloxalyl derivatives in nonoptimized yields ranging from 23 to 90%. The rates of reaction of these and several other lactones with cysteine at pH 7.4 and their KB toxicities were measured. These studies showed that neither the strained trans-fused α-methylene lactone **12** nor the hydroxy-α-methylene lactones **5** and **6** reacted with cysteine with rates comparable to elephantopin. Based on these limited studies, the rate of cysteine addition appears to be relatively insensitive to changes in strain energy and neighboring groups. In addition, the rate constant for reaction with cysteine did not correlate with cytotoxicity.

A number of sesquiterpene lactones or ketones containing an enone system have cytotoxic and, in some cases, significant antitumor activity.[1,2] The activity of these compounds apparently derives from their chemical reactivity which primarily involves the conjugate addition of various nucleophilic thiols resulting in alkylation. Compounds which contain the α-methylene γ-lactone or 2-cyclopentenone groups have demonstrated reactivity with thiol-rich enzymes, including phosphofructokinase[3] and glycogen synthetase,[4] and with simple model thiols

0022-2623/78/1821-0815$01.00/0