5-(Benzyloxy)-1-hydroxy-2,2-indandipropionic Acid δ-Lactone (23). By use of conditions virtually identical with those employed in the reduction of keto acids **3–6, 22** afforded δ-lactone **23**, mp 175–176 °C ($CHCl_3$/benzene/hexane), in 90% yield: IR (KBr) 3400, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.8–7.67 (m, 8 H, aromatic), 5.4 (s, 1 H, C-1 H), 5.05 (s, 2 H, benzylic), 2.95 (s, 2 H, benzylic), 1.25–2.48 (m, 8 H, aliphatic); MS (70 eV), *m/e* 366 (M^+). Anal. ($C_{22}H_{22}O_5$) C, H.

Pharmacological Methods. Female albino CD-1 mice, weighing on average 22 ± 0.2 g and in natural estrous, were sacrified by cervical dislocation. The uterine horns were isolated and prepared for isometric contraction recordings under 200-mg tension in oxygenated tissue baths maintained at 37 °C.[6,14] The composition of the bathing solution was as follows (g/L): NaCl, 8.046; KCl, 0.2; $CaCl_2 \cdot 2H_2O$, 0.132; $MgCl_2 \cdot 6H_2O$, 0.106; $NaHCO_3$, 1.0; $NaH_2PO_4 \cdot H_2O$, 0.065; dextrose, 1.0. Following an equilibration period of 30 min, two 5-min control responses to $PGF_{2\alpha}$ (10^{-7} M) wer obtained, followed each time by a 20-min washout period. The agent to be tested was then added at a given concentration to the bath and left in contact with the tissue for 5 min prior addition of 10^{-7} M $PGF_{2\alpha}$. After recording of the 5-min response to $PGF_{2\alpha}$ in presence of the test agent, the tissue was washed for 20 min with the physiological medium. Recovery of the responsiveness of the tissue to $PGF_{2\alpha}$ was then ascertained by adding 10^{-7} M $PGF_{2\alpha}$ for 5 min. Finally, the tissue was washed for 10 min and the resting tension recorded for 3 min. Control uterine tissues were not exposed to the test compound but were otherwise treated similarly to the test tissues. In these control tissues, the response to $PGF_{2\alpha}$ did not decline with repeated exposure.

In a few experiments, KCl (54 mM) or $BaCl_2$ (2.2×10^{-4} M) was used instead of $PGF_{2\alpha}$ to stimulate the uterine strip.

The integrated contractile force generated by the agonist ($PGF_{2\alpha}$, KCl, or $BaCl_2$) in the presence of the test compound was expressed as a percentage of the mean of the two initial control responses to the agonist recorded prior to addition of the test agent. Recovery responses were expressed similarly.

The test compounds were dissolved in 100 μL of 0.25 N NaOH and diluted with 100 μL of distilled water to pH 7. The agonists and test compounds were added in 10-μL volumes to the 10-mL tissue bath to obtain the desired concentrations.

Registry No. **1**, 68935-40-0; **2**, 90606-30-7; **3**, 90606-31-8; **4**, 78326-94-0; **5**, 80106-55-4; **6**, 90606-32-9; **7**, 90606-33-0; **8**, 90606-34-1; **9**, 78326-92-8; **10**, 90606-35-2; **11**, 90606-36-3; **12**, 90606-37-4; **13**, 90606-38-5; **14**, 90606-39-6; **15**, 90606-40-9; **17**, 90606-41-0; **18**, 90606-42-1; **19**, 90606-43-2; **20**, 78326-88-2; **21**, 90606-44-3; **22**, 90606-45-4; **23**, 90606-46-5; methyl acrylate, 96-33-3.

Potential Synthetic Codeine Substitutes: (–)-3-*O*-Aryl-*N*-methylmorphinans

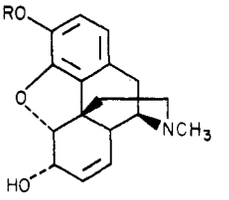
Erno Mohacsi,*† Tom Hayes,† and Jerry Sepinwall‡

Chemical Research Department and Pharmacology Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
Received December 19, 1983

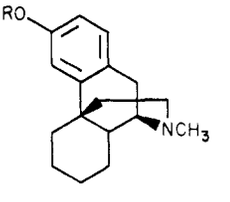
A series of novel *O*-aryl-*N*-methylmorphinans (7–19) were synthesized by the Ullmann reaction from levorphanol (4) in our search for a synthetic codeine (2) substitute with reduced addition liability. The compounds were evaluated for antinociceptive potency and receptor binding affinity. Among these compounds, (–)-3-phenoxy-*N*-methylmorphinan (7) is an orally active analgesic comparable in potency to codeine (2), which exhibits decreased physical dependence liability and longer duration of action.

In recent years, there has been considerable interest in attempting to provide alternative sources for or to replace with synthetic substitutes analgesics prepared from opium.[1] In connection with this latter approach directed at the search for a synthetic codeine (2) substitute with reduced addiction liability, we reported[2] the synthesis of 3-*O*-*tert*-butylmorphine (3) and (–)-3-*tert*-butoxy-*N*-methylmorphinan (6). Our rationale for preparing these novel codeine (2) and levomethorphan (5) analogues was based on the expectation that a tertiary butyl group on the phenolic oxygen would prevent their in vivo metabolic conversion to morphine (1) and levorphanol (4), respectively, thus eliminating the pharmacological effects of these metabolites. Metabolic studies[3] have shown that the tertiary butyl group successfully blocks the enzymatic O-dealkylation of these compounds. However, unlike codeine (2) and levomethorphan (5), the analogues 3 and 6 were only marginally active as analgesics and were unstable under acidic conditions.

We therefore shifted our synthetic efforts toward the preparation of aryl ethers of levorphanol (4). The lipophilic aryl group was expected to facilitate transport while retarding metabolic inactivation. An additional attractive feature of these aryl ethers (7–19) (Table I) was their anticipated chemical stability under conditions which cause degradation of codeine (2) to morphine (1), thus providing a safeguard against abuse.



1, R = H
2, R = CH_3
3, R = $C(CH_3)_3$



4, R = H
5, R = CH_3
6, R = $C(CH_3)_3$
7, R = C_6H_5

Chemistry. The aryl ethers (7–16) in Table I were prepared from 4 by the Ullmann reaction.[4] For example, treatment of 4 with bromobenzene in pyridine in the presence of potassium carbonate and copper gave 7 in 52% yield. The substituted *O*-aryl-*N*-methylmorphinans (8–16) were prepared by this method from 4 and the appropriate aryl halides. O-Demethylation of the methoxyphenyl-substituted analogues 9–11 with pyridine hydrochloride at elevated temperature gave the hydroxyaryl ethers 17–19 without cleavage of the aryl ether bond.

Similarly, when 7 was treated with pyridine hydrochloride at 220 °C for 25 min[5] or with other O-dealkylating

† Chemical Research Department.
‡ Pharmacology Department.

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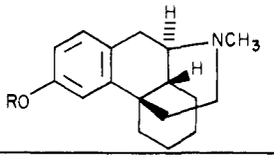
0022-2623/84/1827-1219$01.50/0

Table I. Physical and Biological Data for *O*-Arylmorphinans



no.	R	yield, %	mp, °C (recryst solv)[a]	$[\alpha]^{25}_D$ (*c*, MeOH), deg	formula	anal.[b]	analgesic act.,[c-e] ED_{50}, mg/kg writhing	tail-flick
7	C_6H_5	52	131–133 (A)	−20.08 (0.99)	$C_{23}H_{27}NO{\cdot}C_4H_6O_6$[f]	C, H, N	1.25 (0.78–2.00)[i]	19.71 (17.28–22.16)
8	2-pyridyl	67	137–139 (A)	−7.26 (1.01)	$C_{22}H_{26}N_2O{\cdot}C_4H_6O_6$[f]	C, H, N	1.1 (0.61–1.98)	10.08 (8.95–11.35)
9	4-$CH_3OC_6H_4$	27	170–172 (B)	−34.22 (0.99)	$C_{24}H_{29}NO_2{\cdot}HCl$	C, H, N	2.1 (1.08–4.10)	24.98 (21.99–28.96)
10	3-$CH_3OC_6H_4$	68	148–150 (C)	−39.60 (1.00)	$C_{24}H_{29}NO_2{\cdot}C_2H_2O_4$[g]	C, H, N	2.5 (1.43–4.38)	39.74 (33.21–51.54)
11	2-$CH_3OC_6H_4$	20	185–187 (C)	−37.19 (0.99)	$C_{24}H_{29}NO_2{\cdot}C_2H_2O_4$[g]	C, H, N	0.49 (0.26–0.93)	24.40 (21.27–30.17)
12	4-$CH_3C_6H_4$	48	223–224 (B)	−37.85 (0.69)	$C_{24}H_{29}NO{\cdot}HCl$	C, H, N	23.0 (13.94–37.95)	
13	2-$O_2NC_6H_4$	12	155–157 (B)	−32.62 (0.99)	$C_{23}H_{26}N_2O_3{\cdot}HCl{\cdot}0.5H_2O$	C, H, N	2.8 (1.65–4.48)	
14	4-FC_6H_4	58	162–164 (B)	−34.83 (0.98)	$C_{23}H_{26}FNO{\cdot}HCl{\cdot}0.5H_2O$	C, H, N	1.0 (0.38–2.65)	37.26 (33.15–42.76)
15	3-FC_6H_4	41	121–123 (D)	−18.61 (1.03)	$C_{23}H_{26}FNO{\cdot}C_4H_6O_6{\cdot}0.5H_2O$[f]	C, H, N	1.85 (1.00–3.00)	71.0 (58.36–92.13)
16	2-FC_6H_4	70	180–182 (A)	−30.98 (1.00)	$C_{23}H_{26}FNO{\cdot}C_2H_2O_4$[g]	C, H, N	3.0 (1.36–6.60)	23.31 (20.49–26.98)
17	4-HOC_6H_4	72	160–163 (E)	−34.55 (0.99)	$C_{23}H_{27}NO_2{\cdot}HCl$	C, H, N	1.3 (0.65–2.60)	6.69 (4.88–8.17)
18	3-HOC_6H_4	71	135–138 (E)	−19.21 (1.26)	$C_{23}H_{27}NO_2{\cdot}C_4H_6O_6{\cdot}C_2H_5OH$[h]	C, H, N	9.0 (4.50–18.00)	80.14 (56.17–159.14)
19	2-HOC_6H_4	56	111–112 (A)	−15.96 (1.07)	$C_{23}H_{27}NO_2{\cdot}C_4H_6O_6{\cdot}C_2H_5OH$[h]	C, H, N	1.8 (0.90–3.60)	11.44 (10.95–12.06)

[a] A = EtOH, B = EtOAc, C = EtOAc–Et_2O, D = $(Me)_2CO$, E = EtOH–EtOAc. [b] Analyses of the elements indicated were within ±0.4% of theory. [c] The compounds were administered to the mice subcutaneously in distilled water for the writhing and normal saline solution for the tail-flick tests. [d] For biological data on the reference compounds, see Table II. [e] All biological tests were carried out on the salt indicated. [f] *d*-Tartrate. [g] Oxalate. [h] *d*-Tartrate ethanolate. [i] Numbers in parentheses are the 95% confidence limits obtained by graphical[11] or regression[14] analysis.

Table II. Analgesic Potency and Receptor Binding of *O*-Arylmorphinans

compd	route	analgesic act.,[a] ED_{50}, mg/kg writhing	tail-flick	binding affinities:[g,h] [^{3}H]naltrexone (10^{-9} M) $IC_{50} \times 10^{-6}$ (Tris buffer)
morphine[b]	sc	0.46 (0.26–0.83)[f]	4.06 (3.78–4.41)	0.027
	po	2.5 (1.40–4.45)	31.20 (26.30–35.73)	
codeine[c]	sc	2.3 (1.21–3.91)	38.97 (35.31–42.79)	10.0
	po	24.0 (13.71–42.00)	119.03 (105.16–132.21)	
levorphanol[d]	sc	0.11 (0.06–0.22)	1.21 (1.13–1.31)	0.004
	po	1.40 (0.70–2.80)	8.50 (7.22–10.25)	
levomethorphan[e]	sc	0.64 (0.34–1.22)	6.78 (6.23–7.42)	2.0
	po	1.5 (1.32–1.71)	5.27 (4.49–6.17)	
7[d]	sc	1.25 (0.78–2.00)	19.71 (17.28–22.16)	5.0
	po	2.3 (1.22–4.32)	51.68 (43.72–62.41)	

[a] The compounds were administered sc and po to the mice in distilled water for the writhing test and in normal saline solution for the tail-flick test. [b] Sulfate. [c] Phosphate. [d] Tartrate. [e] Hydrobromide. [f] Numbers in parentheses are the 95% confidence limits obtained by the graphic[11] or regression[14] analysis. [g] Binding was performed with rat brain homogenate. [h] Expressed as the concentration of compound required to inhibit stereospecific [^{3}H]naltrexone binding by 50%. The IC_{50} values are the means of results from three closely similar experiments.

agents commonly employed in the morphine and morphinan series, such as 48% HBr in HOAc for 6 h[6] or BBr_3 in $CHCl_3$ at room temperature,[7] only starting material was isolated. Attempted ether cleavage with sodium in liquid NH_3[8] also resulted in the recovery of **7** in high yield.

Results and Discussion

Tables I and II summarize the results obtained in various test procedures[9–15] with the aryl ethers (**7–19**). Activities of these compounds were compared with those of morphine (**1**), codeine (**2**), levorphanol (**4**), and levomethorphan (**5**). (−)-3-Phenoxy-*N*-methylmorphinan (**7**) showed about twice the analgesic potency of codeine (**2**) in mice. When the phenoxy group in **7** was replaced by a pyridyloxy group **8**, a moderate increase in analgesic activity was observed. Except for the 4-hydroxy analogue **17**, substituents on the phenyl ring did not significantly alter analgesic potency. Because of its chemical simplicity, the phenyl ether **7** was evaluated in other tests.

As shown in Table II, compound **7** interacted with the opiate receptor with an affinity comparable to codeine (**2**) and levomethorphan (**5**).[15,16] The oral analgesic potency of **7** is about 10 times that of codeine (**2**) in the writhing and about twice as active in the tail-flick assay,[12,13] indicating good oral bioavailability. There is a 50% reduction in analgesic activity in the rat tail-flick test[12,13] 90 min after the subcutaneous administration of 25 mg/kg of codeine

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(2). After an equiactive dose of 7, the activity persists for at least 3 h. Additionally, Dewey et al.[17] have demonstrated that 7 substituted significantly less for morphine (1) than did codeine (2) in morphine-dependent rats. In addition, these studies also showed that 7 produces considerably less primary physical dependence in rats in contrast to codeine (2) and morphine (1).[17]

(-)-3-Phenoxy-*N*-methylmorphinan (7) and other aryl ethers of levorphanol (4) are analgesic. The phenoxymorphinan 7 is orally active and comparable in potency to codeine (2) in analgesic tests and opiate receptor bonding but exhibits decreased physical dependence liability and a longer duration of action. Although 7 is a levorphanol ether, it cannot be converted by conventional reactions to levorphanol (4), thus providing a safeguard against illicit conversion to levorphanol (4). Furthermore, since 7 is prepared by total synthesis, adequate supplies can be assured.

Experimental Section

Chemistry. Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were characterized by IR (Beckman IR-9 spectrophotometer), UV (Carey 14-spectrophotometer), and NMR (Varian Associates A-60 and HA-100 spectrometers, Me_4Si internal standard). Specific rotation measurements were performed on a Perkin-Elmer 141 electronic polarimeter. Where analyses are indicated by symbols of the elements, results obtained were within ±0.4% of theoretical values.

(-)-3-Phenoxy-*N*-methylmorphinan (7) *d*-Tartrate. A solution of 10.2 g (0.04 mol) of (-)-3-hydroxy-*N*-methylmorphinan (4) in 240 mL of freshly distilled pyridine was refluxed with stirring under N_2 with 18.5 g (0.118 mol) of bromobenzene, 13.8 g of K_2CO_3, and 13.0 g of copper (granular and electrolytically purified Fisher No. C 434) for 8 days. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between Et_2O (500 mL) and 5 N NaOH (200 mL). The ether solution was washed once with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The crude base 7 on treatment with *d*-tartaric acid in $(Me)_2CO$ gave 10.0 g (52%) of $7 \cdot C_4H_6O_6$.

(-)-3-(2-Pyridyloxy)-*N*-methylmorphinan (8) *d*-Tartrate. Treatment of 2.6 g (0.01 mol) of 4 with 1.7 g (0.01 mol) of 2-bromopyridine in 50 mL of pyridine containing 2.1 g of K_2CO_3 and 2.5 g of Cu for 22 h as described for 7 produced the crude base 8. The base on treatment with *d*-tartaric acid in $(Me)_2CO$ gave 3.3 g (67%) of $8 \cdot C_4H_6O_6$.

(-)-3-(4-Methoxyphenoxy)-*N*-methylmorphinan (9) Hydrochloride. The reaction of 5.1 g (0.02 mol) of 4 with 7.5 g (0.04 mol) of 4-bromoanisole in 20 mL of pyridine containing 4.1 g of K_2CO_3 and 0.2 g of Cu for 7 days was carried out as described for 7 to give the crude base 9. The base was taken up in EtOAc and acidified with EtOAc–HCl. Recrystallization from EtOAc furnished 2.1 g (27%) of 9·HCl.

(-)-3-(3-Methoxyphenoxy)-*N*-methylmorphinan (10) Oxalate. Treatment of 5.1 g (0.02 mol) of 4 with 7.5 g (0.04 mol) of 3-bromoanisole in 20 mL of pyridine containing 4.1 g of K_2CO_3 and 0.2 g of Cu for 10 days as described for 7 gave the crude base 10. The base on treatment with oxalic acid in ether afforded 6.1 g (68%) of $10 \cdot C_2H_2O_4$.

(-)-3-(2-Methoxyphenoxy)-*N*-methylmorphinan (11) Oxalate. Treatment of 5.1 g (0.02 mol) of 4 with 7.5 g (0.04 mol) of 2-bromoanisole in 20 mL of pyridine containing 4.1 g of K_2CO_3 and 0.2 g of Cu for 3 days as described for 7 produced the crude base 11. The base on treatment with oxalic acid in ether afforded 1.8 g (20%) of $11 \cdot C_2H_2O_4$.

(-)-3-(4-Methylphenoxy)-*N*-methylmorphinan (12) Hydrochloride. Reaction of 5.0 g (0.019 mol) of 4 in 20 mL of pyridine with 6.4 g (0.037 mol) of 4-bromotoluene containing 4.0 g of K_2CO_3 and 0.2 g of Cu for 9 days using the reaction conditions given above for 7 produced the crude base 12. The base was taken up in EtOAc and acidified with EtOAc–HCl. Recrystallization from EtOAc furnished 3.5 g (48%) of 12·HCl.

(-)-3-(2-Nitrophenoxy)-*N*-methylmorphinan (13) Hydrochloride Hemihydrate. Reaction of 6.4 g (0.024 mol) of 4 in 30 mL of pyridine with 10.0 g (0.05 mol) of 1-bromo-2-nitrobenzene containing 6.0 g of K_2CO_3 and 0.3 g of Cu for 3 days using the reaction conditions given for 7 produced the crude base 13. The base on treatment with EtOAc–HCl in EtOAc give 1.3 g (12%) of 13·HCl. Crystallization from EtOAc gave pure 13·HCl as the hemihydrate.

(-)-3-(4-Fluorophenoxy)-*N*-methylmorphinan (14) Hydrochloride Hemihydrate. The procedure similar to that for 7 was followed. Treatment of 5.1 g (0.02 mol) of 4 with 17.0 g (0.09 mol) of 4-fluoro-1-bromobenzene in 20 mL of pyridine containing 4.1 g of K_2CO_3 and 0.2 g of Cu for 5 days gave the crude base 14. The base on treatment with EtOAc–HCl in EtOAc gave 4.5 g (58%) of 14·HCl as the hemihydrate.

(-)-3-(3-Fluorophenoxy)-*N*-methylmorphinan (15) *d*-Tartrate Hemihydrate. Reaction of 3.0 g (0.011 mol) of 4 with 2.2 g (0.012 mol) of 3-fluoro-1-bromobenzene in 50 mL of pyridine with 2.4 g of K_2CO_3 and 3.0 g of Cu for 8 days using the reaction conditions given for 7 produced the crude base. The base on treatment with *d*-tartaric acid in $(Me)_2CO$ gave 2.4 g (41%) of $15 \cdot C_4H_6O_6$ as the hemihydrate.

(-)-3-(2-Fluorophenoxy)-*N*-methylmorphinan (16) Oxalate. This compound was prepared in a manner similar to that described for 7. Reaction of 2.0 g (0.007 mol) of 4 with 3.5 g (0.02 mol) of 2-fluoro-1-bromobenzene in 10 mL of pyridine with 2.0 g of K_2CO_3 and 2.0 g of Cu for 2 days gave the crude base 16. The oxalate salt of 16 was crystallized from EtOH to give 2.4 g (70%) of $16 \cdot C_2H_2O_4$.

General Procedure for Ether Cleavage. (-)-3-(4-Hydroxyphenoxy)-*N*-methylmorphinan (17) Hydrochloride. A mixture of 2.0 g (0.005 mol) of 9 and 20.0 g of pyridine hydrochloride was heated at 220 °C with stirring under N_2 for 25 min, cooled in an ice bath, and diluted with water. The mixture was made basic with concentrated NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed, dried ($MgSO_4$), and evaporated. The crude base 17 was taken up in EtOAc and acidified with EtOAc–HCl. Recrystallization of this salt from EtOH–EtOAc gave 1.52 g (72%) of 17·HCl.

(-)-3-(3-Hydroxyphenoxy)-*N*-methylmorphinan (18) *d*-Tartrate Ethanolate. This compound was prepared following the procedure given above for 17, starting from 3.8 g (0.01 mol) of 10. The base on treatment with *d*-tartaric acid in EtOH gave 4.04 g (71%) of $18 \cdot C_4H_6O_6$ as the ethanolate.

(-)-3-(2-Hydroxyphenoxy)-*N*-methylmorphinan (19) *d*-Tartrate Ethanolate. This compound was prepared following the general procedure outlined for 17, starting from 2.5 g (0.007 mol) of 11. The base 19 was converted to the tartrate salt with *d*-tartaric acid, which was crystallized from EtOH–EtOAc to give 2.1 g (56%) of $19 \cdot C_4H_6O_6$ as the ethanolate.

Pharmacological Results. Analgesic potencies were determined by both the tail-flick[12,13] and the phenylquinone writhing methods.[9,10] The results are presented in Tables I and II.

Binding assays were performed in rat brain homogenates as previously described.[15] The concentration of test compound necessary to displace one-half of the stereospecific [^{3}H]naltrexone binding (IC_{50}) is shown in Table II.[16]

Acknowledgment. We acknowledge the contribution and encouragement of the late Dr. W. Leimgruber. We are indebted to Dr. E. J. Simon, Department of Medicine, New York University Medical Center, for the binding affinity data. We are also grateful to D. Kelly, R. Marino, and J. Polsky for their technical assistance. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., for the spectroscopic data and the microanalytical data. Finally, we thank L. Berger for his stimulating suggestions.

Registry No. 4, 77-07-6; 7, 67562-76-9; $7 \cdot C_4H_6O_6$, 74569-98-5; 8, 74464-81-6; $8 \cdot C_4H_6O_6$, 90791-67-6; 9, 67562-50-9; 9·HCl, 67562-51-0; 10, 67562-52-1; $10 \cdot C_2H_2O_4$, 90791-68-7; 11, 67562-54-3;

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11·$C_2H_2O_4$, 90791-69-8; 12, 67562-48-5; 12·HCl, 67562-49-6; 13, 67562-67-8; 13·HCl, 67562-68-9; 14, 67562-71-4; 14·HCl, 67562-72-5; 15, 67562-69-0; 15·$C_4H_6O_6$, 90791-70-1; 16, 67562-73-6; 16·$C_2H_2O_4$, 90822-51-8; 17, 67562-61-2; 17·HCl, 67562-62-3; 18, 67562-63-4; 18·$C_4H_6O_6$, 90822-52-9; 19, 67562-65-6; 19·$C_4H_6O_6$, 90791-71-2; bromobenzene, 108-86-1; 2-bromopyridine, 109-04-6; 4-bromoanisole, 104-92-7; 3-bromoanisole, 2398-37-0; 2-bromoanisole, 578-57-4; 4-bromotoluene, 106-38-7; 1-bromo-2-nitrobenzene, 577-19-5; 4-fluoro-1-bromobenzene, 460-00-4; 3-fluoro-1-bromobenzene, 1073-06-9; 2-fluoro-1-bromobenzene, 1072-85-1.

Synthesis and Antitumor Evaluation of Some Nitrosourea and Nitrogen Mustard Amino Acid Derivatives

Marc Rodriguez,† Jean-Louis Imbach,* and Jean Martinez*‡

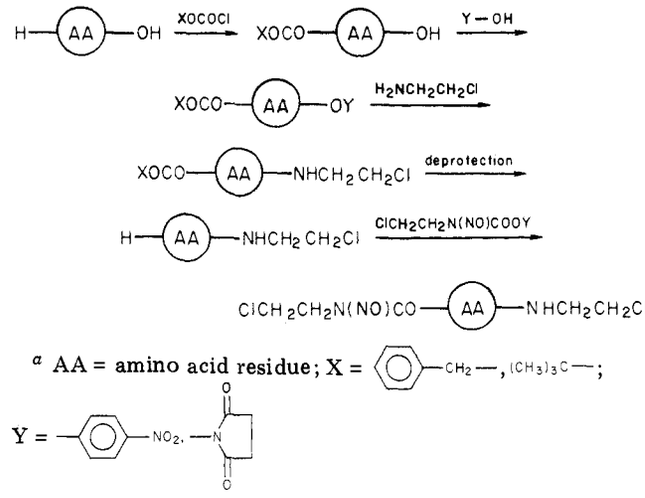
ERA 948 du CNRS, Université des Sciences et Techniques du Languedoc, Place Eugène Bataillon, 34000 Montpellier, France.
Received November 1, 1983

A series of (2-chloroethyl)nitrosourea and nitrogen mustard amino acid derivatives have been synthesized for antitumor evaluation. Reaction of an appropriate N-protected amino acid with 2-chloroethylamine followed by removal of the N-protecting group and condensation with an active (2-chloroethyl)nitrosocarbamate yielded *N*-[(2-chloroethyl)nitrosocarbamoyl]amino acid (2-chloroethyl)amides. Antitumor evaluation was performed against leukemia L1210, in vivo, in mice. These derivatives exhibited very interesting activities, particularly the sarcosine and γ-aminobutyric acid derivatives.

Many nitrosoureas and nitrogen mustard derivatives have been investigated for antitumor activity.[1] Of these compounds, several have proven to be potent antineoplastic agents, in particular, 2-haloethyl derivatives and some of their metabolites showed great promise.[2] For example, 2-[[[(2-chloroethyl)nitrosoamino]carbonyl]-amino]-2-deoxy-D-glucose (CZT, chlorozotocin),[3] *N*-(2-chloroethyl)-*N'*-[2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzoyl)-D-ribofuranosyl]-*N*-nitrosourea (RFCNU),[4] *N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea (CCNU),[5] or *N*,*N'*-bis[(2-chloroethyl)nitrosocarbamoyl]cystamine (CNCC)[6] are some of the most important nitrosourea derivatives in the treatment of tumors. We recently described the synthesis and antitumor evaluations of some "pseudo-peptide" compounds containing covalently bonded cytotoxic units, alkylnitrosoureas at the N-terminus, and/or nitrogen mustard at the C-terminus.[7] These derivatives showed interesting cytotoxic activity on L1210 leukemia, in vivo, in mice. Tang and Eisenbrand reported the preparation of various *N*-[(2-chloroethyl)nitrosocarbamoyl]amino acid derivatives.[8] Suami et al. published the synthesis and antitumor evaluation of (2-chloroethyl)nitrosourea amino acid amide congeners[9] and Montero et al. of their methyl ester derivatives.[10] The antineoplastic activity of these derivatives against L1210 leukemia was quite significant. We herein report the synthesis and antitumor evaluations of some amino acid derivatives bearing two (or three, for polyfunctional amino acids) functional groups—a (2-chloroethyl)nitrosoureido group at the N-terminus end and a (2-chloroethyl)amide group at the C-terminus end.

Chemistry. The synthesis of amino acid (2-chloroethyl)amide derivatives was carried out according to Scheme I. Treatment of a N-protected amino acid active ester (either *p*-nitrophenyl ester[11] or *N*-hydroxysuccinimide ester[12]) with 2-chloroethylamine yielded the N-protected amino acid (2-chloroethyl)amide. In the case of the synthesis of the aspartic acid derivative, a 2 molar excess of 2-chloroethylamine was allowed to react with N-(benzyloxycarbonyl)-L-aspartic acid with use of dicyclohexylcarbodiimide as condensing reagent.[13] Partial deprotection by hydrogenolysis or by trifluoroacetic acid (depending

Scheme I[a]



[a] AA = amino acid residue; X = ; Y =

on the nature of the N-protecting group, benzyloxycarbonyl, Z, or *tert*-butyloxycarbonyl, BOC) and treatment

† This work is part of the Ph.D. thesis of Marc Rodriguez.
‡ Present address: Centre de Pharmacologie Endocrinologie, BP 5055, 34033 Montpellier, France.

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