Synthesis of Imidazolidinediones and Oxazolidinediones from Cyclization of Propargylureas and Propargyl Carbamates

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A synthetic procedure for the preparation of imidazolidinediones by the base-catalyzed cyclization of propargylureas is described. This method appears to be the most versatile way of obtaining these compounds containing tertiary groups substituted on ring-nitrogen number 3. One of these derivatives, 3-*tert*-butyl-5,5-dimethyl-2,4-imidazolidinedione (**1a**), has shown a moderate level of subcutaneous metrazole seizure threshold activity (scMet indicates potential for control of petit mal epileptic seizures) in control screens on mice, as determined by the National Institute of Neurological and Communicative Disorders and Stroke.

Imidazolidinediones (**1**, hydantoins) and oxazolidinediones (**2**) have an extensive history and a myriad of pharmaceutical and industrial uses.[1-3] While many synthetic procedures are available,[1,2,4] few allow incorporation of tertiary alkyl groups on nitrogen in the ring structure. This limitation results from the inability to substitute via an SN_2 process a tertiary substrate after ring formation. One notable exception involves reacting α-lactams (aziridinones) with *N*-cyanoamines.[5,6] It requires, however, that α-lactams of moderate stability be available, a not so trivial prerequisite.[7-9]

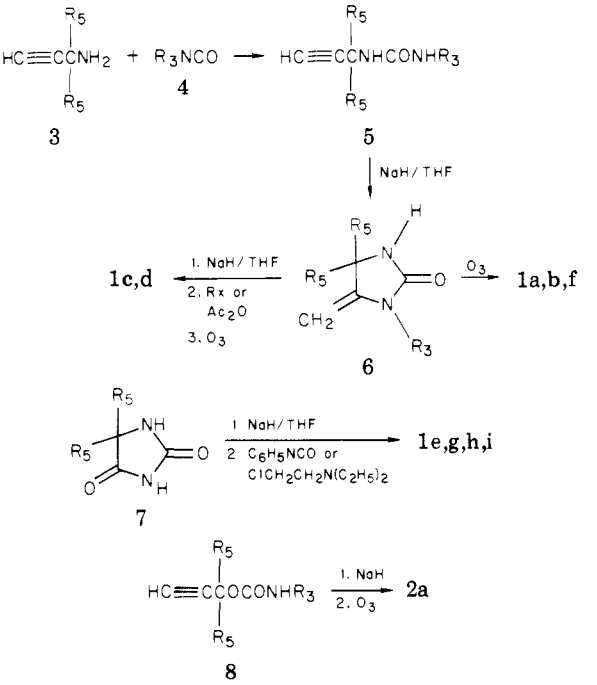
We were interested in developing a general synthetic scheme for the synthesis of oxazolidinediones and imidazolidinediones substituted at position 3 with tertiary alkyl groups, such as *tert*-butyl and adamantyl, to see what effect this had on their anticonvulsant activity. Furthermore, it was of interest to prepare and test substrates with $-CH_2CH_2N(C_2H_5)_2$ units at nitrogen positions 1 and 3. The synthesis and activity of these and several other derivatives are reported herein.

Synthesis. Compounds **1a–i** and **2a** were prepared as shown in Scheme I and all, with the exception of **1a**,[10] **1h**,[11] and **2a**,[12] are new compounds. The latter three were prepared by other methods. Oxazolidinedione **2a** was obtained from the corresponding carbamate.

While the cyclization of propargylureas and propargyl carbamates to give imidazolidinones (**6**) and oxazolidinones is not a new procedure,[13] we can find only one case where a dione derivative (an oxazolidinedione) was prepared in this manner.[14] This synthetic procedure appears to be the most versatile for obtaining hydantoin derivatives with tertiary groups at ring-nitrogen number 3.

Discussion of Activity. Two screens are routinely used to detect anticonvulsant activity. The maximal electroshock seizure test (MES) and the subcutaneous pentylenetetrazol seizure threshold (scMet).[15] A compound's ability to inhibit MES activity has been found to correlate with ability to treat major motor seizures of the grand mal (tonic clonic) type. Control in preventing scMet-type induced seizures indicates potential efficacy in treatment of petit mal (absence) seizures.[15] In general, the hydantoins **1** are most effective in the control of grand mal defects. For example, 5,5-diphenyl-2,4-imidazolidinedione (**1**, R_5 = C_6H_5; R_1, R_3 = H) sold as phenytoin or Dilantin® is the most widely prescribed drug for these seizures. Conversely, barbiturates, e.g., phenobarbital, sodium valproate, and benzodiazepines, e.g., clonazepam, are often prescribed for the latter. Interestingly, phenytoin shows no activity in the scMet screens.[16] Furthermore, it has a wide range of toxic effects,[17] and the search for new derivatives with reduced side effects and increased scMet activity are useful pursuits. It is hoped that the synthetic procedure introduced here might contribute to this end.

Scheme I



All compounds listed in Table I with the exception of **1d** and **1h** failed to show activity in the MES assay.[18,19] The latter displayed an ED_{50}, effective dose on 50% of the test animals, of 80 mg/kg. The former was too toxic to permit assignment of an ED_{50}, $TD_{50} \leq 30$ mg/kg (toxic dose on 50% of screens). Only **1a** was determined to show scMet activity, ED_{50} = 129.7 mg/kg and TD_{50} = 343 mg/kg.

5,5-Diphenyl-2,4-imidazolidinedione is one of the most active hydantoins, as determined by MES techniques (ED_{50} = 9.5 mg/kg),[20] yet shows no scMet activity. Since it is known that replacement of both phenyl groups with methyls, i.e., 5,5-dimethyl-2,4-imidazolidinedione, destroys even the MES activity,[16,19] it was chosen as the model compound to derivatize. It is, thus, surprising to find such a definite level of scMet activity from simple *tert*-butyl substitution at N-3 (**1a**, Table I). This appears to be a specific effect, as one other N-3 tertiary alkyl group, adamantyl (**1b**), had no activity and similar substitution on oxazolidinediones **2a** produced no activity. Further-

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Table I. Properties of Imidazolidinediones and Oxazolidinadione 2a

compd	R_5	R_3	R_1	mp, °C[a]	formula[c]
1a	CH_3	$C(CH_3)_3$	H	147-148	$C_9H_{16}N_2O_2$
1b	CH_3	1-adamantyl	H	194-195	$C_{15}H_{22}N_2O_2$
1c	CH_3	$C(CH_3)_3$	CH_3	81-82	$C_{10}H_{18}N_2O_2$
1d	CH_3	$C(CH_3)_3$	$COCH_3$	53-54	$C_{11}H_{18}N_2O_3$
1e	CH_3	$CONHC_6H_5$	H	172-173.5	$C_{12}H_{13}N_3O_3$
1f	CH_3	$SO_2C_6H_4CH_3$	H	149.5-150.5	$C_{12}H_{14}N_2O_4S$
1g	CH_3	$CH_2CH_2N(C_2H_5)_2$	H	92-93	$C_{11}H_{21}N_3O_2$
1h	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	H	118.5-119.5	$C_{21}H_{25}N_3O_2$
1i	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	$CH_2CH_2N(C_2H_5)_2$	215-217[b]	$C_{27}H_{38}N_4O_2$
2a	CH_3	$-C(CH_3)_3$		69-70	ref 12

[a] Compounds 1a,b,e-h and 2a were recrystallized from $CHCl_3$-hexane; 1c and 1d from pentane. [b] Boiling point (0.1 mm). [c] All compounds were analyzed for C, H, N; analytical results were within ±0.4% of the theoretical values.

more, additional alkylation at N-1 (1c) destroys this activity, and acylation at N-1 (1d) introduces severe toxicity. Amidation (1e), sulfonamidation (1f), and substitution at N-3 by diethylaminoethylene (1g) also produces no activity. The latter group even reduces the MES activity of 5,5-diphenyl-2,4-imidazolidinedione from 9.5 to 80 mg/kg (lit.[11] MES = 122 mg/kg). Similar substitution at N-1 (1i) removes all activity.

While we have no explanation for the tertiary butyl effect, it is interesting to speculate that scMet activity might be introduced in dilantin (5,5-diphenyl-2,4-imidazolidinedione) by similar N-3 substitution, thus alleviating the need for administering two drugs (dilantin + phenobarbital) for control of both types of seizures (absences and tonic-clonic). To this end, the synthesis of 3-*tert*-butyl-5,5-diphenyl-2,4-imidazolidinedione is underway via the scheme outlined herein.

Experimental Section

All melting points are corrected and spectral data (NMR and IR not included) are consistent with structure assignments. **3-*tert*-Butyl-5,5-dimethyl-2,4-imidazolidinedione (1a)** was prepared as described earlier.[10]

3-(1-Adamantyl)-5,5-dimethyl-2,4-imidazolidinedione (1b). Adamantane-1-carbonyl azide[21] (7.5 g, 36.6 mmol) in 50 mL of anhydrous benzene was heated to reflux for 2 h. The mixture was cooled to 0 °C and 3.5 g (42.1 mmol) of 1,1-dimethylpropargylamine in 25 mL of benzene was added dropwise. After heating the mixture at reflux for 2 h, the benzene was removed in vacuo and the residual white solid was recrystallized from methanol to give 7.95 g (76% based on carbonyl azide) of *N*-(1-adamantyl)-*N'*-(1,1-dimethylproparyl)urea (5b), mp 244-245 °C dec.

To 0.6 g (25 mmol) of sodium hydride suspended in 150 mL of dry THF was added 4.0 g (15.4 mmol) of product from above. The mixture was heated at reflux for 5 h, cooled, and quenched by the cautious addition of 100 mL of water. The THF was removed in vacuo and extracted with $CHCl_3$. The $CHCl_3$ was dried (K_2CO_3) and concentrated, and the solid was recrystallized from hexane-$CHCl_3$ to yield 2.75 g (69%) of 1-(1-adamantyl)-5-methylene-4,4-dimethyl-2-imidazolidinone (6b), mp 183.5-184.5 °C. Anal. ($C_{16}H_{24}N_2O$) C, H, N.

Ozone was passed through a solution of 1.0 g (3.8 mmol) of product 6b from above in 50 mL of $CHCl_3$ at 0 °C for 1 h. Water (25 mL) was added to the mixture, and after stirring for 2 h at room temperature the organic layer was separated, dried ($MgSO_4$), and concentrated. The solid residue was recrystallized from hexane-$CHCl_3$ to give 0.62 g (60%) of 1b.

1-Methyl- and 1-acetyl-3-*tert*-butyl-5,5-dimethyl-2,4-imidazolidinedione (1c and 1d) were obtained in 86 and 60% yields from ozonolysis of the corresponding imidazolidinones 6c and 6d.[10]

3-(*N*-Phenylcarbamyl)- and 3-[(diethylamino)ethyl]-5,5-dimethyl-2,4-imidazolidinedione (1e and 1g) and 3-[(diethylamino)ethyl]- and 1,3-bis[(diethylamino)ethyl]-5,5-diphenyl-2,4-imidazolidinedione (1h and 1i) were prepared in 66, 59, 61, and 40% yields, respectively, by treating the sodium salt of the dimethyl- or diphenylimidazolidinedione, formed from NaH in THF, with phenyl isocyanate or β-chloroethyldiethylamine hydrochloride.[22]

5,5-Dimethyl-3-(*p*-toluenesulfonyl)-2,4-imidazolidinedione (1f). To a solution of 5.9 g (71.3 mmol) of 1,1-dimethylpropargylamine in 200 mL of dry hexane was added dropwise 14.1 g (71.6 mmol) of *p*-toluenesulfonyl isocyanate in 100 mL of hexane. After stirring the solution for 3 h, the solid was filtered and recrystallized from ethanol-water (without heating) to give 11.3 g (57%) of *N*-(1,1-dimethylpropargyl)-*N'*-(*p*-toluenesulfonyl)urea (5f), mp 129-131 °C. Anal. ($C_{13}H_{16}N_2O_3S$) C, H, N.

Urea 5f was cyclized to 6f in 46% yield as described in the preparation of 1b, mp (from ethanol-water) 148-149.5 °C. Anal. ($C_{13}H_{16}N_2O_3S$) C, H, N. Ozonolysis of 6f, as described for 1b, gave 1f in a 44% yield.

3-*tert*-Butyl-5,5-dimethyl-2,4-oxazolidinedione (2a). *N*-*tert*-Butylcarbamic acid, 1,1-dimethylpropynyl ester (8a), was prepared from the addition of 2-methyl-3-butyn-2-ol (21.2 g, 0.25 mol) to *tert*-butyl isocyanate (21.7 g, 0.22 mol) in ether. After distillation of the solution, 16.3 g (35%) of ester was obtained, which crystallized on standing: bp 93-97 °C (1(mm); mp 36-37 °C. Anal. ($C_{10}H_{17}NO_2$) C, H, N.

3-*tert*-Butyl-5,5-dimethyl-4-methylene-2-oxazolidinone was prepared by sodium hydride cyclization of the ester as described for the ureas. From 10 g (54.6 mmol) of ester was obtained 9.7 g (97%) of oxazolidinone as an unstable solid (mp 57-59 °C), which was used in the next step without further purification.

Oxazolidinone was ozonolyzed as described above to give 4.85 g (49%) of 2a.

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Antiallergy Activity of Substituted 11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acids

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A series of substituted 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acids were prepared and evaluated as antiallergy agents. Several analogues were orally active. 2-Methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinoazoline-8-carboxylic acid (**6**) was superior to cromolyn sodium and doxantrazole orally and intravenously in the rat PCA test and a rat allergic bronchospasm model.

A new orally active antiallergy agent was recently reported having the structure 11-oxo-11*H*-pyrido[2,1-*b*]-quinazoline-8-carboxylic acid.[1] A series of substituted 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acids have been prepared and compared with two clinically effective antiallergy agents, cromolyn sodium and doxantrazole. While cromolyn sodium is ineffective orally, it is useful insufflated as a powder. Doxantrazole has been reported to be an orally active antiallergy agent in humans.[2]

The reversible narrowing of bronchial airways and accompanying edema in bronchial mucosa observed in asthma may be caused by a specific allergic response or by a nonspecific irritant. β-Adrenergic bronchodilators, anticholinergics, theophylline, or steroids are useful for symptomatic relief. An alternate approach is the use of an antiallergy agent, such as cromolyn sodium, which appears to act by preventing the release of histamine and other possible allergic mediators resulting from antibody–antigen interactions.[3]

We report the synthesis and effects of substitution on the antiallergy activity of a series of oxopyrido[2,1-*b*]-quinazoline-8-carboxylic acids.

Chemistry. The 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acids were prepared in one step from 6-chloronicotinic acid and the appropriately substituted anthranilic acid by refluxing the mixture in glacial acetic acid[4] (method A) or ethanol containing hydrochloric acid (method B). Compounds **8** and **18** were prepared from their corresponding methoxy analogues **10** and **16** utilizing a pyridine hydrochloride fusion method (method C).[5]

The alkoxy derivatives **11**–**15** were prepared from **4** by alkylation with an alkyl halide and potassium carbonate (method D).

Discussion

The substituted pyrido[2,1-*b*]quinazolinones were evaluated for their antiallergy activity by their ability to inhibit passive cutaneous anaphylaxis (PCA) in rats as described in the Experimental Section.[6] Those agents which showed an inhibition greater than 50% at 0.5 mg/kg iv were studied further for their ID_{50} and oral efficacy. Since the 8-carboxylic acid **1** was more active than the corresponding 6 and 7 isomers,[1] the effects of aromatic substitution upon biological activity were studied in a series of 8-carboxylic acids. The activities are summarized in Table I.

The most potent analogues of the series were **4**–**6**, **13**, and **16**. However, **4**, **13**, and **16** were less active orally compared with **5** and **6**. Replacement of the methoxy group of **5** by ethoxy, hydroxyethoxy, propoxy, butoxy or allyloxy (**11**–**15**) resulted in reduced oral activity. In the rat PCA test, **6** is about 30 times more potent than cromolyn sodium and doxantrazole intravenously (Table I). Orally, **6** is 4–6.7 times better than doxantrazole, while cromolyn sodium is inactive orally. When analogue **6** was compared with cromolyn sodium and doxantrazole in the rat allergic bronchospasm model,[7] **6** was ten times more potent orally than doxantrazole in preventing death in 50% of the animals (ID_{50}) and 4.6 times better in preventing the fall in respiratory flow rate by 40% (ID_{40}). All three agents effectively inhibit the anaphylactic histamine release from rat mast cells[6,9] (Table II).

Analogue **6** is not a histamine antagonist, since it did not inhibit histamine-induced contractions of the guinea pig ileum[8] at concentrations up to 10^{-4} M.

In summary, several 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acids are orally active antiallergy agents which prevent anaphylactic reactions in both skin and pulmonary tissues of rats. 2-Methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid (**6**) appears to be superior to other known antiallergy agents, cromolyn sodium, and doxantrazole.

Experimental Section

Rat Reaginic Passive Cutaneous Anaphylaxis (PCA). The PCA test[6] involved immunization of rats with 1 mg of ovalbumin intramuscularly and approximately 10^{10} *B. pertussis* organisms as pertussis vaccine, intraperitoneally. Fourteen days later, the rats were bled and serum was prepared. Suitable dilutions of antiserum were injected intradermally at various sites on the back of rats 48 h before an intravenous injection of 1 mg of ovalbumin in 1 mL of physiological saline and 0.25% Evan's Blue. Thirty

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