final volume of 2 ml, were incubated at 37° in a shaking water bath. Standard bacterial plate counts of each tube were made and plates incubated in an atm of 10% CO_2 for 48 hr when the viable plate count was determined.

2,3-Dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3a) and 6-chloro-2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3b) were prepared as reported previously.[1]

2,3-Dihydro-6-nitro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3c). A mixt of 2-amino-5-nitrobenzamide (2.3 g, 0.012 mole) and 5-nitro-2-thiophenecarboxaldehyde (2.0 g, 0.012 mole) in 40 ml of EtOH was treated with 1 ml of concd HCl. The reaction mixt was boiled under reflux with stirring for 2 hr. After chilling overnight in the refrigerator, the mixt was filtered to give a yellow solid (2 g, 52%).

Dissolving the crude compound in hot EtOH–DMF (charcoal) and diluting with H_2O until turbidity persisted provided analytically pure material which melted at 210–211°. *Anal.* ($C_{12}H_8N_4O_5S$) C, H, N.

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DL-1-(α-Methylbenzyl)-2-methylimidazole-5-carboxylate Esters. Synthesis and Pharmacological Properties

Erik F. Godefroi* and J. Th. J. Platje

Department of Organic Chemistry, The University of Technology, Eindhoven, The Netherlands. Received September 24, 1971

Certain 1-substituted imidazole-5-carboxylic acid esters have, in the past, been shown to display significant biological activity. For example 1-arylalkylimidazole-5-carboxylate esters of type I induce a potent and short-acting hypnosis in the rat;[1a,b] cyclized variants of I, such as II, exhibit significant antimycotic activity against dermatophytes.[2a,b]

R = alkyl; substituted alkyl
R' = H, CH₃, C₂H₅
x = 1, 2
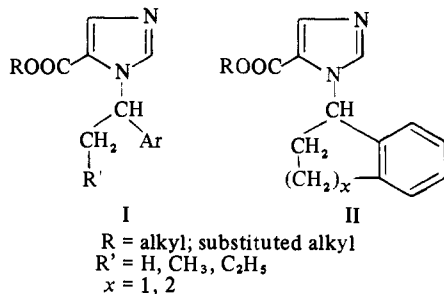
These compounds were made essentially according to Jones;[3] this method precluded the preparation of 2-alkylimidazole homologs. The conceivable metabolic vulnerability of this position prompted preparation of a few 2-Me analogs (III). The synthesis and gross pharmacological properties of 8 and 9 are now reported.

Chemistry. Efforts to synthesize 2-β-aminoethylimidazole


8, R = CH₃
9, R = C₂H₅
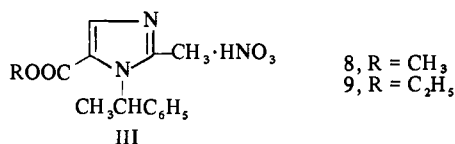
("isohistamine") had led Jones[4] to base his approach on the reaction of 1-benzyl-2-chloromethylimidazole with KCN in absolute EtOH. Recent work by Roe, *et al.*,[5] proves beyond a doubt that Jones' purported 1-benzyl-2-cyanomethylimidazole (1) was, in fact, 1-benzyl-2-methylimidazole-5-carbonitrile (2). Such anomalous substitution patterns are not uncommon in heterocyclic chemistry.†
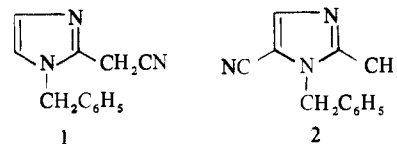
With these considerations in mind, 4 was made as follows. Reaction of α-methylbenzyl chloride with the Na salt of imidazole in DMF‡ followed by hydroxymethylation of the crude reaction mixture afforded 3; this was converted to the chloromethyl hydrochloride 4 by means of $SOCl_2$. The original Jones procedure for preparing "1" (*i. e.*, 2) called for the use of KCN–absolute EtOH. We chose to treat 4 with 2 equiv of NaCN in "80% acetone," thereby avoiding alcoholysis of 4. The reaction was carried out at room temp. Upon ir examination of the crude reaction mixture the presence of 2 nitriles was apparent. Separation of these components was facile and practical, as they differed in basicity. The main product (47%), isolated as the HCl salt, was identified as 5; *ca.* 10% of the desired nitrile 6 was obtained as base from the mother liquor. Characterization of 5 and 6 was predicated upon analytical and spectral data (see Experimental Section).

Hydrolysis of 6 to 7 was monitored by the rate of NH_3 evolution. This was slow under ordinary hydrolytic conditions (5 *N* NaOH; alcoholic KOH); more vigorous conditions (KOH–ethylene glycol) made the reaction proceed more rapidly but the yield of 7 was unsatisfactory (*ca.* 50%). Recourse was eventually taken to a 2-step procedure. Treatment of nitrile 6 with MeOH–HCl gave (presumably) the corresponding Me ester and/or the imino ether. Subsequent basic hydrolysis then gave acid 7 in very good yield.

Compd 7 was converted to the corresponding acid chloride by means of $SOCl_2$. Esters 8 and 9 were then obtained by methanolysis and ethanolysis of the acid chloride. They were isolated and tested as nitrate salts.

3, X = OH; Y = H
4, X = Cl, Y = H (·HCl)
5, X = CN; Y = H (·HCl)
6, X = H; Y = CN
7, X = H; Y = COOH
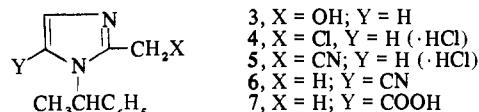
Pharmacology.§ Compds 8 and 9 were tested on mice for behavioral effects, anticonvulsant properties, and lethality. Results are summarized in Table I. The compounds in question resemble pharmacologically the general anaesthetics, as doses causing loss of righting reflex lie close to those effecting loss of corneal and spinal reflexes. No convulsions were noted upon high-level administration of the compounds. At nonhypnotic doses, 8 (75 mg/kg ip) and 9 (100 mg/kg ip) slightly potentiated the hypnotic effect of sodium phenobarbital.[7]

Experimental Section

Melting points were taken on a Fisher-Johns block and are uncorrected. Analytical samples had ir and nmr spectra compatible

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†See literature citations of ref 5.
‡Reaction conditions were analogous to the benzylation of imidazole.[6]
§Pharmacological data were kindly furnished by Dr. V. Claassen, Department of Pharmacology, N. V. Philips-Duphar, Weesp, The Netherlands.

Table I.

Effect	ED_{50}, mg/kg 8	ED_{50}, mg/kg 9
Loss of muscle tone	100	24
Loss of righting reflex	132	200
Loss of corneal reflex	152	~214
Loss of spinal reflex	168	~238
Anticonvulsant activity (metrazol)	68	68
Anticonvulsant activity (MES)	100	147
LD_{50} (48 hr)	563	320

with assigned structures; combustion values for C, H, and N were within 0.4% of theory.

DL-1-(α-Methylbenzyl)imidazole-2-methanol (3). To a soln of 52 g (2.25 g-atoms) of Na in 600 ml of MeOH was added 170 g (2.50 moles) of imidazole. Most of the solvent was distilled off whereupon 450 ml of DMF was added and solvent removal was resumed till the internal temp reached 125°. The mixture was cooled to 30°. Addition of 327 g (2.32 moles) of α-methylbenzyl chloride resulted in an exothermic reaction, which required cooling. The reaction was then allowed to proceed overnight. Benzene (ca. 2 l.) was added and the soln was scrubbed 5 times with H_2O. The product was extracted from the organic phase with 3 N HCl and was regained from the acidic aqueous phase by basification. It was extracted into C_6H_6. Drying of the organic phase and removal of solvent left 160 g (42%) of an oil. To this residue was added 800 ml of CH_2O (37%) and the solution was refluxed for 72 hr. Excess reagent was removed by distillation until stopping up of the system became bothersome. PhMe and H_2O were then added whereupon more of the aqueous phase was removed azeotropically. The mixt was cooled, basified, and stirred for 1 hr, and the phases were separated. Extraction of the aqueous phase with fresh PhMe, drying of the combined organic layers, and stripping of solvent left a residue which was rendered crystalline by addition of Me_2CO; yield 93 g (50%), mp 88-92°. An analytical sample (Me_2CO) had mp 94-96°; nmr (CF_3COOH) τ 5.00-5.06 (d, 2, $ImCH_2OH$), 2.4-3.0 (m, 7, C_6H_5 and $C_3H_2N_2$). *Anal.* ($C_{12}H_{14}N_2O_2$) C, H, N.

DL-1-(α-Methylbenzyl)-2-chloromethylimidazole Hydrochloride (4). A soln of 150 g (0.74 mole) of 3 in 700 ml of $SOCl_2$ was refluxed for 1 hr. Addition of i-Pr_2O to the cloud point, cooling, and filtration afforded 177 g of 4. A recrystallized sample (i-PrOH–i-Pr_2O) had a decomposition point of ~260°; nmr (CF_3COOH) τ 5.22 (s, 2, $ImCH_2Cl$). *Anal.* ($C_{12}H_{13}ClN_2 \cdot HCl$) C, H, N.

Reaction of 4 with NaCN in 80% Acetone. Compd 4, 177 g (0.69 mole), was dissolved in 200 ml of H_2O at 60°; to this was added 1.1 l. of Me_2CO. The resulting saturated soln was added dropwise and with stirring to a slurry of 72 g (1.48 moles) of NaCN in 75 ml of H_2O (Caution: Good ventilation is necessary. HCN is liberated). Stirring was continued overnight whereupon 850 ml of Me_2CO was distilled out of the reaction flask. Benzene (700 ml) was then added. Inorganic material was removed from this mixture by repeated scrubbing with H_2O whereby the organic phase was kept in the flask, aqueous phases being withdrawn by aspirator suction. The C_6H_6 layer was dild with 1 l. of i-Pr_2O, and saturated HCl–i-PrOH was added cautiously until further addition failed to produce cloudiness. Cooling of this mixt gave semisolid HCl salts from which solvent was removed by decantation. Subsequent trituration (Me_2CO) rendered one component crystalline. This was filtered off, yielding 79 g (47%) of material characterized as DL-1-(α-methylbenzyl)-2-cyanomethylimidazole hydrochloride (5). An analytical sample was recrystallized from i-PrOH–i-Pr_2O; mp 180-185°; nmr (CF_3COOH) τ 5.60 (s, 2, $ImCH_2CN$), 2.31-2.91 (m, 7, arom H); ir (KBr) 2262 cm⁻¹ (C≡N). *Anal.* ($C_{13}H_{13}N_3 \cdot HCl$) C, H, N.

The trituration liquors (vide supra) were evaporated. The residue, taken up in H_2O was basified (NaHCO₃) and seeded to give solid DL-1-(α-methylbenzyl)-2-methylimidazole-5-carbonitrile (6). Upon filtration and trituration (Me_2CO), 14.8 g (10%) of material was obtained. Recrystallization (Me_2CO–i-Pr_2O) furnished analytical material; mp 106-107°; nmr τ 7.22 (s, 3, $ImCH_3$), τ 2.4-2.9 (m, 5, (C_6H_5), τ 2.01 (s, 1, ImH); ir (KBr) 2235 cm⁻¹ (C≡N). *Anal.* ($C_{13}H_{13}N_3$) C, H, N.

DL-1-(α-Methylbenzyl)-2-methylimidazole-5-carboxylic Acid (7). A soln of 10 g (0.047 mole) of 6 in 100 ml of MeOH was alternately saturated with HCl gas and refluxed (2 hr). After 3 such cycles followed by a final 18-hr reflux period, the solvent was removed and was replaced with a soln of 20 g of NaOH in 50 ml of H_2O. The mixt was refluxed for another 3 hr; addition of a soln of

30 g of AcOH in 50 ml of H_2O, seeding, and cooling provided 9.4 g (87%) of 7; mp 203-205°. Analytical material (H_2O) had mp 208-209°; nmr τ 7.64 (s, 3, $ImCH_3$). *Anal.* ($C_{13}H_{14}N_2O_2 \cdot H_2O$) C, H, N.

DL-1-(α-Methylbenzyl)-2-methylimidazole-5-carboxylic Acid Methyl Ester Nitrate (8). A mixt of 3.0 g of acid 7 and 20 ml of $SOCl_2$ was refluxed for 1 hr. Excess reagent was removed and was replaced with 30 ml of MeOH. Refluxing (1 hr) and solvent evaporation left an oil which was taken up in H_2O. The soln was treated with K_2CO_3 from which the product base was extracted into Et_2O. Addition of HNO_3 to the dried ethereal soln furnished 3.7 g of product; mp 92-94°. It was recrystallized from MeOH–Me_2CO–i-Pr_2O to melt at 93-94°; ir (KBr) 1745 cm⁻¹ (C=O). *Anal.* ($C_{14}H_{16}N_2O_2 \cdot HNO_3$) C, H, N.

DL-1-(α-Methylbenzyl)-2-methylimidazole-5-carboxylic acid ethyl ester nitrate (9), prepared analogously to 8, had mp 143-144° (EtOH–i-Pr_2O). *Anal.* ($C_{15}H_{18}N_2O_2 \cdot HNO_3$) C, H, N.

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Cysteine Scavengers. 1. Bis(3-pyridylmethyl) Phosphate and Bis(3-pyridylmethyl) Pyrophosphate†

Mervyn Israel,* Marilyn A. Whitesell, Edward J. Modest, George E. Foley, Herbert Lazarus, and Franz Bergel‡

The Children's Cancer Research Foundation and the Departments of Biological Chemistry and Pathology, Harvard Medical School, Boston, Massachusetts 02115. Received July 21, 1971

A recent report[1] on the absolute nutritional requirement *in vitro* of lymphoblastic leukemic cells of human origin for L-cysteine (or L-cystine) prompted us to consider the synthesis of modified transport forms of pyridoxal for use as an enzymomimetic system for cysteine desulfhydrase.[2] In connection with the synthesis of bis(pyridoxalyl) phosphate and bis(pyridoxalyl) pyrophosphate, 2 key target compounds in this investigation, we chose as a model compound for study 3-pyridylmethanol, which, like pyridoxal, possesses a carbinol function at the β position on the pyridine nucleus. We should like now to report the preparation of the hitherto unknown bis(3-pyridylmethyl) phosphate (1)