Central Nervous System Depressants. II.[1a] 1-Aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-ones[1b]

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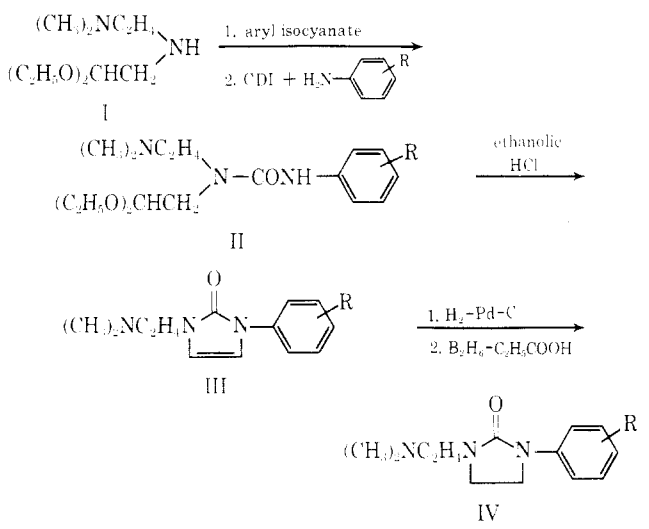
1-Aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-ones have been prepared by the cyclization of [3-aryl-1-(2-dimethylaminoethyl)ureido]acetaldehyde diethyl acetals. These compounds were reduced catalytically or with diborane–propionic acid to 1-aryl-3-(2-dimethylaminoethyl)-2-imidazolidinones. The 4-imidazolin-2-ones were inactive as CNS depressants.

In the previous paper,[1a] we reported that 1-aminoalkyl-3-aryl-2-imidazolidinones exhibit potent CNS-depressant activity when tested in laboratory animals.[2] Extending this work, we have now investigated a series of 1-aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-ones, which are Δ^4-unsaturated analogs of the previous compounds.

The 4-imidazolin-2-ones were prepared by a modification of the procedure of Luckenbaugh[3] (Chart I).

CHART I



Compound I, [(2-dimethylaminoethyl)amino]acetaldehyde diethyl acetal, was treated with an aryl isocyanate or with N,N′-carbonyldiimidazole (CDI) and an aniline derivative to form [3-aryl-1-(2-dimethylaminoethyl)ureido]acetaldehyde diethyl acetals (II and Table I) in nearly quantitative yield. These compounds were heated for 2 hr with dilute hydrochloric acid, cyclization occurred, and good yields of 1-aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-ones (III and Table II) were obtained.

When III was catalytically hydrogenated using 10% palladium-on-carbon catalyst, 1-aryl-3-(2-dimethylaminoethyl)-2-imidazolidinones (IV and Table III) were obtained. In this way the previously unreported *m*-amino, 3,4-dimethoxy, 3,4,5-trimethoxy, and 3,4-methylenedioxy analogs were prepared.

This method of reduction was unsatisfactory for the preparation of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (imidoline) because partial dehalogenation occurred during the hydrogenation. However, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one was satisfactorily reduced to imidoline in 85% yield when the diborane–propionic acid method of Brown and Murray[4] was used.

Nmr spectra were determined for 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone and for 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one. In each case, the spectrum showed the expected pattern (see Experimental Section).

Pharmacological Results.—The compounds described in this paper were screened for CNS-depressant activity by the previously described methods.[1] 1-(*m*-Aminophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride was moderately active in reducing locomotor activity and rod-walking ability, whereas all of the other compounds were inactive. The inactivity of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one is in marked contrast to the strong depressant activity of the analogous 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone.[1]

Experimental Section

General procedures are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in the tables, and critical variations in the procedures are noted in the table footnotes. Temperatures are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 137 Infracord. Nmr spectra were determined in $CDCl_3$ on a Varian A-60 instrument. Chemical shifts (δ) are reported relative to tetramethylsilane (δ = 0.00, internal standard).

[(2-Dimethylaminoethyl)amino]acetaldehyde Diethyl Acetal.—The literature procedure of Jones, *et al.*,[5] was followed for this compound. The yield of product, bp 115–125° (20 mm), was 77%.

Anal. Calcd for $C_{10}H_{24}N_2O_2$: C, 58.8; H, 11.8; N, 13.7. Found: C, 58.7; H, 11.9; N, 13.6.

[3-Aryl-1-(2-dimethylaminoethyl)ureido]acetaldehyde Diethyl Acetal Derivatives (Table I). Procedure A.—A solution of 0.05 mole of [(2-dimethylaminoethyl)amino]acetaldehyde diethyl acetal in 25 ml of hexane was added dropwise with stirring to a solution of 0.05 mole of the appropriate aryl isocyanate dissolved in 25 ml of hexane. The reaction was exothermic. The mixture was stirred for about 1 hr and then heated at reflux temperature

(1) (a) Previous paper in this series: W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966); (b) presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) Several *m*-halo derivatives have been of particular interest and the compound, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (imidoline), has been chosen for evaluation in man.

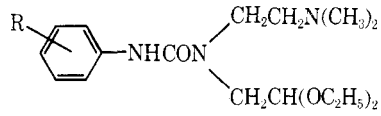
(3) (a) R. W. Luckenbaugh, U. S. Patent 3,133,079 (May 12, 1964); (b) R. W. Luckenbaugh, U. S. Patent 3,148,211 (Sept 8, 1964).

(4) H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).

(5) R. G. Jones, E. C. Kornfeld, K. C. McLaughlin, and R. C. Anderson, *ibid.*, **71**, 4000 (1949).

Table I

Ureidoacetaldehyde Acetals

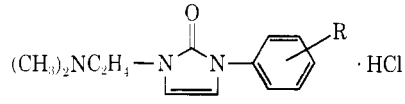


R	Yield, %	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	96[a]	$C_{17}H_{29}N_3O_3$	63.1	63.0	9.0	9.2			13.0	12.8
m-Cl	98[a]	$C_{17}H_{28}ClN_3O_3$	57.1	56.8	7.9	7.9	9.9	10.7	11.7	11.6
p-Cl	96[a]	$C_{17}H_{28}ClN_3O_3$	57.1	57.4	7.9	8.1	9.9	10.1	11.7	11.8
p-F	100[a]	$C_{17}H_{28}FN_3O_3$	59.8	59.7	8.3	8.2	5.6	6.0	12.3	12.7
m-NO_2	100[a,b]	$C_{17}H_{28}N_4O_5$	55.4	55.2	7.7	7.7			15.2	15.6
3,4,5-$(CH_3O)_3$	92[c]	$C_{20}H_{35}N_3O_6$	58.1	58.1	8.5	8.4			10.2	9.8
3,4-OCH_2O	84[c]	$C_{18}H_{29}N_3O_5$	58.8	58.4	8.0	8.2			11.4	11.8

[a] Procedure A. [b] Benzene was used as solvent. [c] Procedure B. The compounds in this table were viscous oils.

Table II

4-Imidazolin-2-one Hydrochlorides[a]

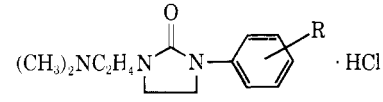


R	Yield, %[b]	Mp, °C	Recrystn solvent[c]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	37	173–174	A	$C_{13}H_{18}ClN_3O$	58.3	58.0	6.8	7.0	13.2	13.2	15.7	15.9
m-Cl	46	170–171[d]	B	$C_{13}H_{17}Cl_2N_3O$	51.7	51.6	5.7	5.7	23.5	23.3	13.9	13.7
p-Cl	48	203–205	A	$C_{13}H_{17}Cl_2N_3O$	51.7	51.5	5.7	5.8	23.5	23.2	13.9	13.7
p-F	56	203–204	A	$C_{13}H_{17}ClFN_3O$	54.6	54.7	6.0	6.3	12.4	12.5	14.7	15.1
m-NO_3	86	213–215[e]	A	$C_{13}H_{17}ClN_4O_3$	49.9	50.1	5.5	5.7	11.3	11.1	17.9	17.8
3,4-$(CH_3O)_2$	28	169–170	B	$C_{15}H_{22}ClN_3O_3$	55.0	54.8	6.8	7.2	10.8	10.7	12.8	12.5
3,4,5-$(CH_3O)_3$	51[f]	141–143[g]	A	$C_{20}H_{27}N_3O_8$[g]	54.9	54.9	6.2	6.3			9.6	9.6
3,4-OCH_2O	45	218–220	A	$C_{14}H_{18}ClN_3O_3$	53.9	53.9	5.8	6.0	11.4	11.3	13.5	13.6

[a] Procedure C. [b] Purified hydrochlorides unless otherwise noted. [c] A, ethanol; B, ethanol–ether. [d] The base melts at 61–62°. [e] The base melts at 87–89°. [f] Base, mp 122–124°. [g] Maleate.

Table III

2-Imidazolidinone Hydrochlorides[a]



R	Yield, %[b]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	63	190–191[c,d]	$C_{13}H_{20}ClN_3O \cdot 0.5H_2O$	56.0	56.1	7.6	7.8	12.7	13.0	15.1	15.3
m-Cl	85[e]	217–219[c,f]	$C_{13}H_{19}Cl_2N_3O$	51.3	51.2	6.3	6.3	23.3	23.1	13.8	13.4
m-NH_2	54[g]	197–199[c]	$C_{13}H_{21}ClN_4O$	54.8	54.7	7.4	7.3	12.5	12.5	19.7	19.3
3,4-$(CH_3O)_2$	34	177–179[h]	$C_{15}H_{24}ClN_3O_3$	54.8	55.1	7.4	7.6	10.8	10.8	12.8	12.8
3,4,5-$(CH_3O)_3$	70	200–201[c]	$C_{16}H_{26}ClN_3O_4$	53.4	53.6	7.3	7.4	9.9	10.1	11.7	11.8
3,4-OCH_2O	58	235–237[c]	$C_{14}H_{20}ClN_3O_3$	53.6	53.6	6.4	6.4	11.3	11.3	13.4	13.5

[a] Procedure D. [b] Purified hydrochlorides, crude yields were generally much higher. [c] Recrystallized from ethanol. [d] Lit.[1] mp 191–193°. [e] Base prepared by procedure E. [f] Lit.[1] mp 217–219°. [g] Prepared by reduction of the *m*-nitro analog. [h] Recrystallized from ethanol–ether.

for 30 min. The hexane was removed by distillation under reduced pressure and the residue, a viscous oil, was analyzed and treated in the next step without further purification.

Procedure B.—A solution of 0.03 mole of the aniline derivative in 75 ml of benzene was distilled until the distillate was clear, in order to remove any moisture from the reagents. A solution of 5.7 g (0.032 mole) of 90% N,N′-carbonyldiimidazole in 75 ml of dry THF was added rapidly with stirring and cooling. The mixture was stirred at room temperature for 2 hr and then treated with a solution of 0.03 mole of [(2-dimethylaminoethyl)amino]-acetaldehyde diethyl acetal in 45 ml of THF. The reaction mixture was stirred at room temperature for 1 hr, heated at reflux temperature for 1 hr, and then concentrated to remove the solvents. The residue was shaken with benzene, and the benzene solution was extracted three times with 25-ml portions of saturated salt solution. The benzene extracts were concentrated under reduced pressure, and the residue, a viscous oil, was analyzed and allowed to react in the next step without further purification.

4-Imidazolin-2-one Hydrochlorides (Table II). General Procedure C.—A mixture of 0.02 mole of the [3-aryl-1-(2-dimethylaminoethyl)ureido]acetaldehyde diethyl acetal, 10 ml of ethanol, and 20 ml of 2 *N* HCl was heated at reflux temperature for 2 hr and concentrated to remove the solvent. The residue was made alkaline by the addition of about 25 ml of 5 *N* NaOH, and the mixture was extracted with benzene. Some K_2CO_3 was added to the aqueous layer and it was again extracted with benzene. The benzene extracts were combined, dried ($MgSO_4$), and concentrated. The residue, generally semicrystalline, was dissolved in ether and treated with an excess of 2 *N* ethanolic HCl. The hydrochloride salt was separated by filtration or by decantation of the liquid layer and was purified by recrystal-

lization from ethanol or an ethanol–ether mixture; nmr spectrum of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one: δ 7.8–7.1 (aromatic protons, complex multiplet, 4 H), 6.62 and 6.42 (C-4 H and C-5 H, AB quartet, $J_{4,5}$ = 3 cps, 2 H), 3.73 ($CH_2NC{=}O$, triplet, J = 6 cps, 2 H), 2.60 (CH_2NMe_2, triplet, J = 6 cps, 2 H), 2.27 ($N(CH_3)_2$, singlet, 6 H).

Imidazolidinone Hydrochlorides (Table III). General Procedure D.—A mixture of 0.01 mole of the 1-aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-one hydrochloride, 100 ml of 85% ethanol, and 1 g of 10% Pd–C catalyst was shaken in a Parr hydrogenator under about 3.05 kg/cm² of hydrogen pressure for 1.5–3 hr. The reaction mixture was filtered and the mother liquor was concentrated to remove the solvents. The residue was triturated with acetone or ether until crystallization occurred. The crystals were filtered off and recrystallized from ethanol or an ethanol–ether mixture.

Procedure E. Reduction of 1-(*m*-Chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one Using Diborane.—A solution of 1 *M* borane in THF (3 ml, 0.003 mole) was added to a cooled mixture of 400 mg (0.0015 mole) of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one and 8 ml of diglyme. The solution was left at room temperature for 20 hr and then heated in an oil bath at 170–180° for 2 hr. The mixture was cooled, 3 ml of propionic acid was added, and the reaction mixture was again heated at 170–180° for 1 hr. The mixture was concentrated to remove the solvent, 5 ml of 5 *N* NaOH was added, and the product was extracted into ether. The ether layer was washed with salt solution and concentrated. The residue weighed 0.35 g, and vapor phase chromatography indicated that this was greater than 95% 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone. The product was converted to the hydrochloride, mp 217–219° after recrystallization from ethanol, identical by mixture melting point and infrared spectra with the compound previously prepared by alkylation of 1-(*m*-chlorophenyl)-2-imidazolidinone;[1] nmr spectrum of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone: δ 7.8–6.8 (aromatic protons, complex multiplet, 4 H), 3.9–3.4 (C-4 and C-5 CH_2, multiplet, 4 H), 3.35 (CH_2NCO, triplet, J = 6 cps, 2 H), 2.47 (CH_2NMe_2, triplet, J = 6 cps, 2 H), 2.25 ($N(CH_3)_2$, singlet, 6 H).

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New Psychotropic Agents. VII.[1] 5H-Dibenzo[*a*,*d*]cycloheptenyl Sulfones

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5H-Dibenzo[*a*,*d*]cyclohepten-5-one and the 10,11-dihydro derivative were converted to their alkylene dithioketals which were oxidized to the corresponding tetroxides. Interaction of the ethylene thioketal tetroxides with amines gave 5-(5H-dibenzo[*a*,*d*]cycloheptenyl) 2-aminoethyl sulfones which may be considered as analogs of amitriptyline. Related benzhydryl sulfones were prepared employing hydrazine and 2-dimethylaminoethanol. The compounds possessed only slight biological activities.

Certain aminoalkyl benzhydryl sulfones have been reported to possess central nervous system activity. Thus Archer and Suter[2] have claimed anticonvulsant effect for a number of 2-(disubstituted amino)ethyl benzhydryl sulfones. The preparation of related compounds containing a 5H-dibenzo[*a*,*d*]cycloheptene nucleus in place of the benzhydryl group was of interest. These could be considered as analogs of the antidepressant drug amitriptyline (10,11-dihydro-N,N-dimethyl-5H-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine) in which the methinyl carbon atom of the alkylidene side chain has been replaced by a sulfonyl group.

Several synthetic routes to the sulfones were considered. The benzhydryl compounds have been prepared[2,3] from the interaction of benzhydryl mercaptan with an alkylene chlorobromide followed by oxidation to the corresponding chloroalkyl sulfone and replacement of the chlorine atom by a secondary amino group; attempted oxidations of 2-piperidinoethyl benzhydryl sulfide were unsuccessful. A projected use of 10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5-thiol as a starting material for the tricyclic sulfones was not pursued in view of the report[4] that this thiol could not be obtained by the usual thiourea synthesis with the corresponding 5-chloro compound. An attempt was made to prepare a simple sulfone from this same 5-chloro compound through interaction with ethanethiol under alkaline conditions with subsequent oxidation of the resulting sulfide; none of the desired 5-ethylsulfonyl derivative was obtained. It was obvious that a quite different approach was required and this was found in a novel application of a known reaction, namely, the cleavage of 1,2-disulfones by nucleophilic reagents.[5] Thus Kuhn and Neugebauer[6] obtained 2-piperidinoethyl benzhydryl sulfone in 85% yield by heating 2,2-diphenyl-1,3-dithiolane 1,1,3,3-tetroxide (IV) with piperidine. The interaction of related spirodisulfones containing the dibenzocycloheptenyl nucleus (II) with secondary amines gave the desired basic sulfones (III) in generally good yields (see Tables I and II and Scheme I). The reactions were carried out by heating either with an excess of amine alone or in an appropriate solvent; the normeperidine derivative (IIIe) was prepared from one equivalent of the amine in boiling toluene containing pyridine. The products, best handled as the free bases, tended to retain solvent of crystallization and gave only fair analytical values.

The compounds could not be sublimed *in vacuo* without decomposition. The spectral data were, however, in accord with the proposed structures.

(1) Part VI: M. A. Davis, F. A. Sunahara, F. Herr, and R. Gaudry, *J. Med. Chem.*, **6**, 513 (1963).

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(6) R. Kuhn and F. A. Neugebauer, *Chem. Ber.*, **94**, 2629 (1961).