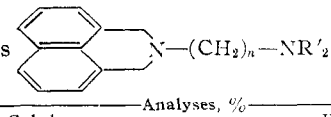
TABLE IV

2-(TERT-AMINOALKYL)-2,3-DIHYDRO-1-BENZ[DE]ISOQUINOLINES



NR′₂	n	Salt	B.p., °C.	Mm.	$n^{25}D$	Formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N[b]	Cl
$N(C_2H_5)_2$	2	..	162–165	0.5	1.5791	$C_{18}H_{24}N_2$			10.44				10.04	
$N(CH_3)_2$	3	..	154–156	0.5	1.5870	$C_{17}H_{22}N_2$	80.26	8.72	11.02		79.73	8.59	10.76	
$N(CH_3)_2$	3	HCl	275[a]			$C_{17}H_{24}Cl_2N_2$	62.38	7.39		21.66	62.37	7.21		21.15[c]
NC_4H_8[d]	3	..	175–180	0.3	1.5970	$C_{19}H_{24}N_2$			9.99				9.42	
NC_4H_8[d]	3	HCl	275[a]			$C_{19}H_{26}Cl_2N_2$	64.58	7.42		20.07	64.99	7.56		20.05[e]

[a] Melting point (decomposition), °C. [b] By titration for basic nitrogen. [c] By titration for ionic halogen. [d] Pyrrolidino group. [e] Microanalysis for total halogen.

D. Reaction of N-Ethyltetrahydroisoquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XVIII.—An isopropyl alcohol solution of 5.2 g. (0.032 mole) of the base and 8.4 g. (0.032 mole) of the bromide was refluxed for 30 hours on the steam-bath. The product, which crystallized out of the cooled solution, was recrystallized from ethanol to yield 10.3 g. (76%) of XVIII, m.p. 240° dec.

E. Reaction of 7-Quinolinol with 3-Bromopropyltrimethylammonium Bromide. Compound XXVI.—An acetonitrile solution of 1.0 g. (0.0069 mole) of 7-quinolinol[26] and 2.7 g. (0.01 mole) of the bromide was refluxed for 16 hours, during which time no precipitate formed. The solution was concentrated to a small volume and the resultant precipitate was recrystallized twice from alcohol–ether to yield 0.45 g. (16%) of green-tinted crystals, m.p. 234° dec.

F. Reaction of 8-Methoxyquinoline with 3-Bromopropyltrimethylammonium Bromide. Compound XXVIII.—A solution of 5.1 g. (0.032 mole) of 8-methoxyquinoline and 8.4 g. (0.032 mole) of the bromide in 25 ml. of acetonitrile was refluxed for 24 hours. The precipitate was recrystallized twice from *n*-propyl alcohol and ether to yield 3.5 g. (26%) of XXVIII, bright yellow crystals, m.p. 177° dec.

(26) C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **66**, 1166 (1944).

Reaction of Isoquinoline with 3-Chloropropyldimethylamine Hydrochloride. Compound X.—A mixture of 20.6 g. (0.13 mole) of 3-chloropropyldimethylamine hydrochloride[2] and 33.6 g. (0.26 mole) of isoquinoline in 500 ml. of isopropyl alcohol was refluxed for 40 hours on the steam-bath. A small amount of insoluble material was removed and the filtrate was concentrated under reduced pressure to a smaller volume, diluted with ethyl acetate and the precipitated solid collected. After four recrystallizations from isopropyl alcohol, a yield of 8.6 g. (23%) of the product, m.p. 214–215° (with preliminary softening), was obtained.

Catalytic Hydrogenation of II. Compound XIX.—A solution of 10.0 g. (0.026 mole) of II in 100 ml. of absolute methanol was hydrogenated over 0.5 g. of platinum oxide at 50 p.s.i. Hydrogen absorption was complete in 15 minutes. The filtered solution was concentrated to about 50 ml. and diluted with ethyl acetate until just cloudy. On cooling there was obtained 7.2 g. (72% yield) of XIX, m.p. 198–203°.

Acknowledgment.—The authors wish to thank the Messrs. D. L. Miller and D. F. Cortright of these laboratories for performing the ionic halogen and basic nitrogen determinations.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Some Spirohydantoins and Ureas Derived from Alkylamino-substituted Alicyclic Ketones

BY GEORGE W. SMITH AND ALLAN R. DAY

RECEIVED DECEMBER 15, 1954

A number of spirohydantoins and ureas derived from alkylamino-substituted alicyclic ketones have been prepared as potential anticonvulsants. The Bucherer method was used for the preparation of the hydantoins. 2-Benzylaminomethylcyclohexanone gave a 2-benzylhexahydro-7a-hydroxyphthalimidine instead of the expected hydantoin. The cleavage of certain Mannich bases during reductive amination has been demonstrated.

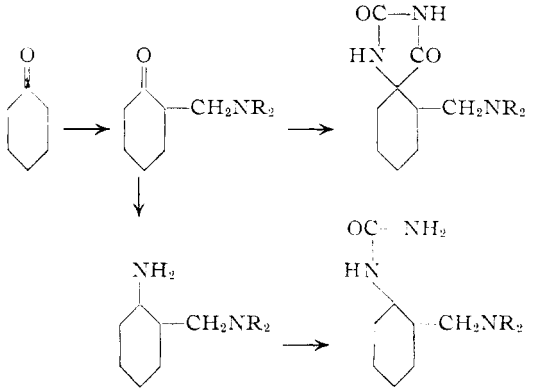
Since the discovery that 5-ethyl-5-phenylhydantoin was active as an anticonvulsant, a large amount of work has been reported on the preparation and testing of 5,5-disubstituted hydantoins. Spirohydantoins derived from alicyclic ketones have been reported also.[1] Recently spirohydantoins prepared from 1-menthone[1a] and carvomenthone[1c] were shown to possess promising anticonvulsant activity when administered to mice. Further testing has shown that these compounds are not useful for controlling convulsions in man. No toxic symptoms, however, were observed in man even when the compounds were administered in very large doses.

(1) (a) A. R. Day and C. F. Kelly, *J. Org. Chem.*, **4**, 101 (1939); (b) R. Tiffeneau and M. Beauvallet, *Presse Med.*, **51**, 417 (1943); (c) E. S. Rothman and A. R. Day, THIS JOURNAL, **76**, 111 (1954).

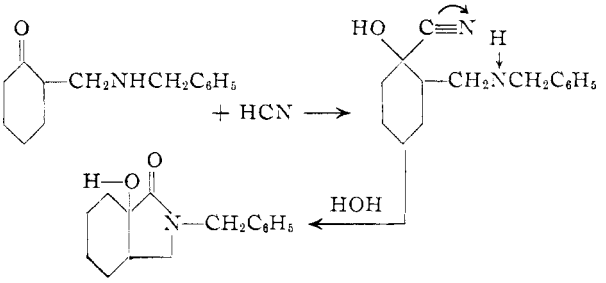
In view of the low water solubility of the above spirohydantoins and the fact that large amounts must be administered for anticonvulsant activity, the preparation of derivatives which possessed increased solubility in water seemed desirable. To accomplish this purpose basic side chains were introduced into appropriate ketones by means of the Mannich reaction and the resulting amino ketones converted to the corresponding spirohydantoins by the Bucherer method.[2] Closely related to the amino-substituted spirohydantoins are the corresponding amino-substituted ureas. Two examples of this type of compound were prepared also. The amino-substituted ureas were made from the

(2) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

amines obtained by the reductive amination of certain Mannich bases.

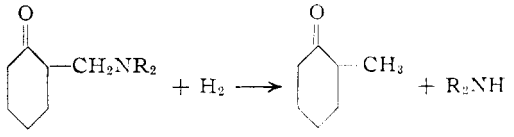


An attempt to prepare a spirohydantoin from 2-benzylaminomethylcyclohexanone led to the formation of what is believed to be 2-benzylhexahydro-7a-hydroxyphthalimidine.



This reaction is similar to the formation of lactams from γ-amino acids. This type of reaction is only possible for 2-alkylaminomethylcyclohexanones. Since the desired spirohydantoin could not be obtained, no further examples of this type were tried.

A significant side reaction which occurred during the reductive amination of Mannich bases was the cleavage of the Mannich base to form the corresponding ketone and amine. This reaction was demonstrated by the isolation of one or both of the cleavage products.



The hydrogenolyses of several Mannich bases, under more vigorous experimental conditions, have been reported recently.[3]

Experimental

Preparation of Mannich Base Hydrohalides. 2-Morpholinomethylcyclohexanone Hydrochloride.—This Mannich base hydrochloride was prepared according to Harradence and Lions.[4]

2-Pyrrolidinomethylcyclohexanone Hydrochloride.—A mixture of 176.0 g. (1.80 moles) of cyclohexanone, 25.5 g. (0.359 mole) of freshly distilled pyrrolidine, 31.0 g. (0.377 mole) of 37% formalin solution and 30 ml. of concentrated hydrochloric acid was agitated vigorously and heated gently for 15 minutes. The mixture was then heated at 80–90° for 20 minutes. It was extracted with 250 ml. of water and the water solution extracted with ether to remove excess ketone. The water was removed under reduced pressure, the residue washed with anhydrous ether and recrystallized from ethyl acetate (6 parts) and ethanol (1 part).

2-Piperidinomethylcyclohexanone Hydrochloride.—This compound was prepared according to the directions of Mannich and Honig.[5]

2-Dimethylaminomethylcyclohexanone Hydrochloride.—This compound was prepared by the method of Mannich and Braun.[6]

2-Benzylaminomethylcyclohexanone Hydrobromide.—This product was prepared by the procedure of Mannich and Hieronimus.[7]

2-Morpholinomethyl-3-methyl-6-isopropylcyclohexanone Hydrochloride.—This compound was prepared by the procedure of Lions and Gill.[8] These workers isolated this product as its quaternary methyl iodide derivative. In the present study, the hydrochloride was purified by repeated recrystallization from acetone (4 parts) and ethyl alcohol (1 part).

Preparation of Spirohydantoins.—The Bucherer method[2] was used for the preparation of the following hydantoins from the corresponding ketones.

6-(Morpholinomethyl)-1,3-diazaspiro[4.5]decane-2,4-dione.—The crude product was recrystallized from 50% alcohol. When this preparation was carried out in a solution approximately one-fourth as concentrated as in a normal Bucherer reaction, a lower melting form of the spirohydantoin was obtained. It was not studied any further.

6-(Pyrrolidinomethyl)-1,3-diazaspiro[4.5]decane-2,4-dione.—The reaction mixture was heated for only 2.5 hours in this case. The crude product was recrystallized from 50% alcohol.

6-(Piperidinomethyl)-1,3-diazaspiro[4.5]decane-2,4-dione.—The crude product was recrystallized from anhydrous ethyl alcohol.

6-(Dimethylaminomethyl)-1,3-diazaspiro[4.5]decane-2,4-dione.—The crude product was recrystallized from 50% alcohol.

6-(Morpholinomethyl)-7-methyl-10-isopropyl-1,3-diazaspiro[4.5]decane-2,4-dione.—In this case the mixture was heated for 34 hours and small amounts of potassium cyanide and ammonium carbonate were added from time to time to compensate for losses by volatilization. The resulting solution was evaporated *in vacuo* and the residue extracted with hot acetone. The acetone was removed by distillation and the oily residue dissolved in hot benzene and diluted with petroluem ether. The resulting crystals were recrystallized from benzene–alcohol and finally from 50% alcohol.

2-Benzylhexahydro-7a-hydroxyphthalimidine.—From 2-benzylaminomethylcyclohexanone, no hydantoin was formed. Only the phthalimidine was isolated. After heating the mixture for 10 hours, the temperature was raised to 70° for 10 hours and finally to 76° for 1 hour. The solution was evaporated under reduced pressure and the residue extracted with hot acetone–benzene. The latter solution was kept at 0° until crystallization was complete. The product was recrystallized from 60% alcohol with the aid of decolorizing carbon and finally from 50% alcohol, yield 27%, m.p. 135–136°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.14; H, 7.71; N, 5.96.

Preparation of Diamine Dihydrochlorides.—These compounds were prepared by the reductive amination of the corresponding ketones.

General Procedure. 1-Amino-2-dimethylaminomethylcyclohexane.—A cooled solution of 15.4 g. (0.08 mole) of 2-dimethylaminomethylcyclohexanone hydrochloride in 110 ml. of dry ethanol was saturated with ammonia gas. The solution was then hydrogenated over palladium on alumina as a catalyst. The solvent was removed under reduced pressure, the residue taken up in water and cooled to 0°. Hydrochloric acid was added to a *p*H of 2 and the solution extracted with ether. The aqueous solution was evaporated under reduced pressure. The oily residue was dis-

(3) E. M. Schultz and J. B. Bicking, THIS JOURNAL, **75**, 1128 (1953).

(4) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).

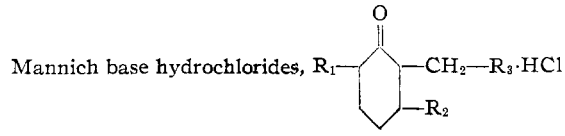
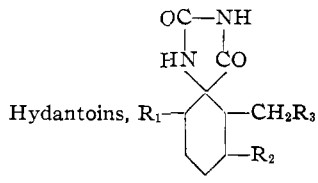
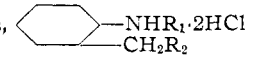
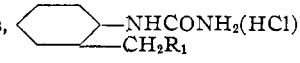
(5) C. Mannich and P. Honig, *Arch. Pharm.*, **265**, 598 (1927).

(6) C. Mannich and R. Braun, *Ber.*, **53B**, 1874 (1920).

(7) C. Mannich and O. Hieronimus, *ibid.*, **75B**, 49 (1942).

(8) F. Lions and N. S. Gill, THIS JOURNAL, **72**, 3468 (1950).

TABLE I

R_1	R_2	R_3	Yield,[a] %	M.p.,[b] °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Mannich base hydrochlorides, 											
H	H	Morpholino	62	144–145[c]	$C_{11}H_{19}NO_2Cl$	56.52	56.59	8.63	8.45	5.99	6.03
H	H	Piperidino	90	161–162[d]	$C_{12}H_{22}NOCl$	62.18	62.20	9.57	9.45		
H	H	Dimethylamino	62	150–150.5	$C_9H_{18}NOCl$	56.38	56.41	9.46	9.42	7.31	7.26
H	H	Pyrrolidino	31.8	142–143	$C_{11}H_{20}NOCl$	60.67	60.58	9.26	9.17	6.43	6.46
Isopropyl	Methyl	Morpholino	15	135.8–136.8	$C_{15}H_{28}NO_2Cl$[e]	62.15	62.00	9.74	9.75	4.83	4.81
Hydantoins, 											
H	H	Morpholino	84	219.8–224.3	$C_{13}H_{21}N_3O_3$[f]	58.40	58.25	7.92	7.79	15.72	15.73
H	H	Morpholino	43.8	210.7–212.7	$C_{13}H_{21}N_3O_3$[g]	58.40	58.50	7.92	7.75	15.72	15.48
H	H	Piperidino	63.1	214.7–216.2	$C_{14}H_{23}N_3O_2$	63.37	63.37	8.74	8.58		
H	H	Dimethylamino	53.3	222.6–227.9	$C_{11}H_{19}N_3O_2$	58.64	58.44	8.50	8.58	18.65	18.72
H	H	Pyrrolidino	62	243.1–245.6	$C_{13}H_{21}N_3O_2$	62.12	62.26	8.42	8.37	16.72	16.58
Isopropyl	Methyl	Morpholino	10	266.5–267.5[h]	$C_{17}H_{29}N_3O_3$	63.13	62.95	9.04	8.85	12.99	13.17
Diamine dihydrochlorides, 											
H	Dimethylamino		36	214.5–215.5	$C_9H_{22}N_2Cl_2$	47.16	47.11	9.68	9.65	12.23	12.24
H	Morpholino		41.6	256.0–257.5	$C_{11}H_{24}N_2OCl_2$	48.71	48.74	8.92	8.82	10.33	10.38
H	Piperidino		30	245.0–246.0	$C_{12}H_{26}N_2Cl_2$	53.52	53.42	9.73	9.71	10.40	10.30
Cyclohexyl	Dimethylamino		20	179.0–181.0	$C_{15}H_{32}N_2Cl_2$	57.86	57.92	10.36	10.41	9.00	8.90
Cyclohexyl	Morpholino		56.5	258[i]	$C_{17}H_{34}N_2OCl_2$	57.78	57.67	9.70	9.82	7.93	7.97
β-Methoxyethyl	Morpholino		25	168.0–170.0	$C_{14}H_{30}N_2O_2Cl_2$	51.06	51.08	9.18	8.91	8.51	8.45
Ureas, 											
Dimethylamino			70	124.5–125.5	$C_{16}H_{21}N_3O$	60.26	60.18	10.62	10.73	21.09	21.26
Morpholino			28	181.1–182.0	$C_{12}H_{24}N_4O_2Cl$	51.88	51.74	8.71	8.60	15.13	15.17

[a] Yields are based on material of reasonable purity and do not take into account the recovery of starting materials. [b] M.p. data are corrected and correspond to the analytically pure samples. [c] Harradence and Lions[4] reported a m.p. of 128° for this compound. [d] After melting, this compound appeared to solidify and finally melted completely at 227°. Similar results were reported by Mannich and Honig.[22] [e] The hydrochloride derivative of this compound has not previously been reported. [f] High melting form. [g] Low melting form. [h] This compound gradually decomposed from 252° finally turning black at 266.5–267.5°. [i] This compound first began to change at 180° but a complete melt was not realized until 258° was reached.

solved in 30 ml. of dry ethanol and distilled to remove water. After three such distillations, a solid product was obtained. It was finally purified by dissolving in hot methanol followed by the careful addition of hot acetone.

1-Amino-2-morpholinomethylcyclohexane Dihydrochloride.—In this case the reaction was carried out in 50% ethyl alcohol and the crude product was recrystallized from ethanol.

1-Amino-2-piperidinomethylcyclohexane Dihydrochloride.—The general procedure was used for the preparation of this compound.

1-Cyclohexylamino-2-dimethylaminomethylcyclohexane Dihydrochloride.—This compound was obtained from 2-dimethylaminomethylcyclohexanone hydrochloride using cyclohexylamine in place of ammonia. In this case after removing the solvent the residue was dissolved in hot acetone containing a little ethanol and the solution kept at −10° for 4 days. The crystals so obtained were recrystallized twice from a 2:1 acetone–alcohol solution.

2-Cyclohexylamino-2-morpholinomethylcyclohexane Dihydrochloride.—This product was prepared from 2-morpholinomethylcyclohexanone hydrochloride and cyclohexylamine.

1-β-Methoxyethylamino-2-morpholinomethylcyclohexane Dihydrochloride.—In this preparation β-methoxyethylamine and 2-morpholinomethylcyclohexanone hydrochloride were the starting materials.

Preparation of Urea Derivatives. 2-Morpholinomethylcyclohexylurea Hydrochloride and 2-Dimethylaminomethyl cyclohexylurea.—A solution of 2.69 g. (0.033 mole) of potassium cyanate in 4 ml. of water was added to a solution of 4.5 g. (0.017 mole) of 1-amino-2-morpholinomethylcyclohexane dihydrochloride in 6 ml. of water. After 30 minutes the solution was heated to 70–80° for 45 minutes, then cooled and filtered. The filtrate was evaporated and the residue extracted with hot alcohol. Removal of the alcohol left a sirup which was taken up in dry ether and treated with dry hydrogen chloride. The product was recrystallized from methanol–acetone.

2-Diethylaminomethylcyclohexylurea was made from 1-amino-2-dimethylaminomethylcyclohexane dihydrochloride and potassium cyanate. In this case the sirup was treated with dry ether which converted it to a solid. The latter was recrystallized from acetone and then from benzene.

PHILADELPHIA, PENNA.