[CONTRIBUTION FROM THE RESEARCH DIVISION, ETHICON, INC.]

The Synthesis and Structure of Spiroimidazolones[1]

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A number of derivatives of 1,3-diazaspiro[4.5]dec-1-en-4-one and 1,3-diazaspiro[4.5]dec-2-en-4-one were prepared by the interaction of appropriately substituted 1-aminocyclohexanecarboxamides and ethyl orthoformate. The structure of these spiroimidazolones was confirmed by chemical interconversions to known materials and by examination of their ultraviolet and infrared spectra. Two compounds previously[3] reported to possess the spiroimidazolone structure appear to be the isomeric 1-formylaminocyclohexanecarbonitriles XII and XIII.

As part of a program directed toward the synthesis of central nervous system depressants we investigated a series of spiroimidazolones of types I and II. Derivatives of 1,3-diazaspiro[4.5]dec-2-en-4-one (I) were prepared by the reaction of ethyl orthoformate and appropriately substituted 1-aminocyclohexanecarboxamides[4] which were obtained by hydrolysis of the corresponding nitriles.[5] The reaction proceeded quite readily and in high yield with alkylaminocyclohexanecarboxamides; the synthesis of 1-arylimidazolones required prolonged reaction periods.

When 1-aminocyclohexanecarboxamide itself was subjected to the ethyl orthoformate reaction, two products could be isolated. One of the materials was the expected unsubstituted spiroimidazolone I or II (R = H) whose structure is discussed in greater detail in the section dealing with spectral data. The other product appeared to be a diethoxymethyl derivative II [R = $CH(OC_2H_5)_2$] resulting from the further interaction of the spiroimidazolone with one mole of ethyl orthoformate. The relationship between the two products became apparent when mild acid hydrolysis of the diethoxymethyl derivative yielded I or II (R = H) while treatment of the latter with ethyl orthoformate resulted in its reconversion to II [R = $CH(OC_2H_5)_2$]. Furthermore by adjusting the excess of orthoformate used in the original reaction mixture one material could be prepared to the exclusion of the other. The assignment of structure II [R = $CH(OC_2H_5)_2$] to the diethoxymethyl derivative is based on spectral data (*vide infra*). Carrington *et al.*[3] some time ago reported two compounds to which they assigned structures II (R = H) and I (R = CH_3). These materials had been prepared by dehydration of compounds, presumed to be 2-hydroxy-4-imidazolidones (III), which in turn had been obtained by the Raney nickel reduction of the corresponding 2-thiohydantoins. Unexpectedly, some of the physical properties of Carrington's spiroimidazolones were quite different from those exhibited by the materials obtained by us in the ethyl orthoformate reaction:

	I or II (R = H)	I (R = CH_3)
Carrington's Compounds	M.p. 94–95°	B.p. 85°/0.1 mm.
Products from ethyl orthoformate reaction	M.p. 165–166°	M.p. 120–121°

The English workers,[3] furthermore, alkylated their *N*-unsubstituted imidazolone with methyl iodide in the presence of silver oxide and obtained a liquid product to which they assigned the 5(4H)-imidazolone structure II (R = CH_3). In contrast, when we treated 1-aminocyclohexane-*N*-methylcarboxamide with ethyl orthoformate, a solid material, m.p. 51–52° was isolated as major reaction product.

Because of these obvious discrepancies it became necessary to ascertain the structure of the compounds that we had obtained *via* the ethyl orthoformate procedure as well as to reinvestigate Carrington's materials.

Since 1,3-diazaspiro[4.5]decanone-4 (IV. R = H) is formed as a by-product in the catalytic desulfurization of 2-thio-1,3-diazaspiro[4.5]decanone-4,[3] it seemed of interest to examine the reduction of our spiroimidazolone I or II (R = H). Indeed, when this compound was subjected to catalytic hydrogenation it was readily converted to the spiroimidazolidone IV (R = H) whose identity was established by comparison (mixed melting point determination, infrared spectrum) with an authentic sample.[6]

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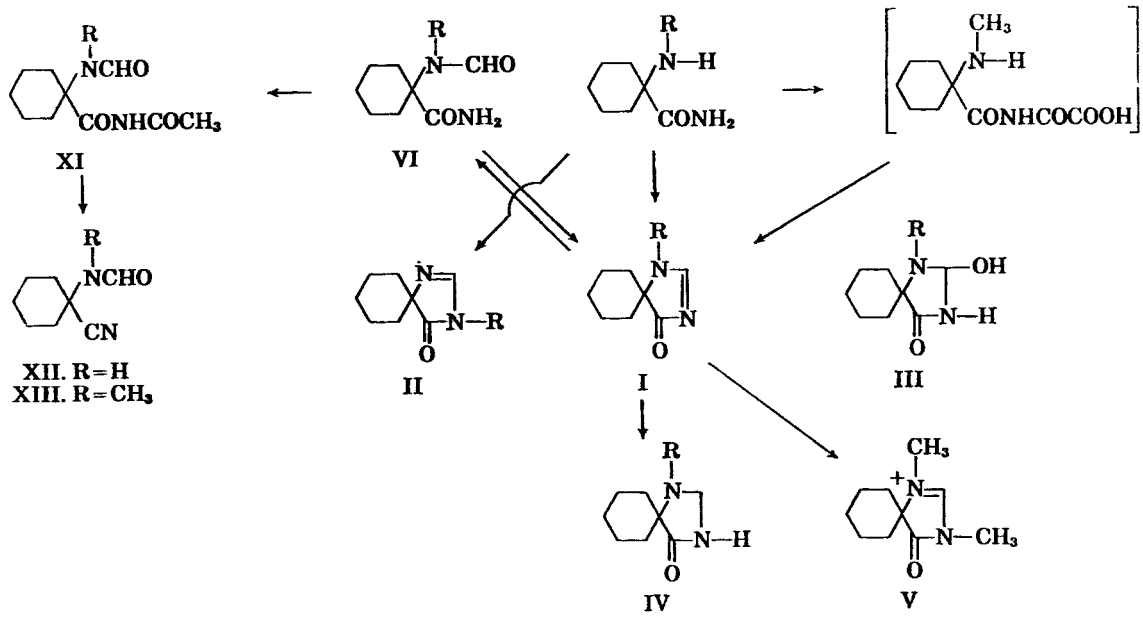
(2) (a) Present address: Shulton, Inc., Clifton, N. J. (b) Present address: The Celanese Corp. of America, Summit, N. J.

(3) H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, 3105 (1953).

(4) E. Schipper and A. R. Day, *J. Am. Chem. Soc.*, 74, 350 (1952); J. Brunken and G. Bach, *Chem. Ber.*, 89, 1363 (1956).

(5) (a) R. L. Betts, R. Muspratt, and S. G. P. Plant, *J. Chem. Soc.*, 1310 (1927); (b) A. H. Cook and S. F. Fox, *J. Chem. Soc.*, 2334 (1949).

(6) We are indebted to Dr. W. S. Waring, Imperial Chemical Industries, Limited, Pharmaceutical Division, Alderley Park, Macclesfield, Cheshire, Great Britain, for supplying a number of samples for purposes of comparison and for communicating to us spectral data which corroborated our findings.



When Carrington's[3] methylation procedure was applied to our spiroimidazolone I or II (R = H), only a methiodide V could be isolated.

In contrast to Carrington's alleged imidazolones which could be recrystallized unchanged from water,[3] our compounds I or II (R = H) and I (R = CH_3) readily took up a mole of water when their aqueous solutions were refluxed briefly. The resulting products proved to be identical with Carrington's 2-hydroxy-4-imidazolidones III (R = H and CH_3).

Some time ago, Whalley *et al.*[7] suggested that 5,5-dimethyl-2-hydroxy-4-imidazolidone[3] possibly exists as its open chain tautomer–α-formylamino-isobutyramide. Subsequently Behringer and Schmeidl[8] reported Raney nickel reduction of 5-alkyl or aralkyl-2-thiohydantoins in moist tetrahydrofuran as a general method for the preparation of α-*N*-formylaminoamides. In view of these reports the infrared spectra of Carrington's[3] 2-hydroxy-4-imidazolidones III (R = H or CH_3) were examined and the compounds were found to exist in their solid state (potassium bromide pellets) as the open chain tautomers VI (R = H or CH_3). This conclusion is based on the findings in the C=O stretching region: Compound VI (R = H) exhibits four peaks corresponding to primary amide I and II bands (1660 cm.$^{-1}$ and 1615 cm.$^{-1}$) and to secondary amide I and II bands (1707 cm.$^{-1}$ and 1535 cm.$^{-1}$). Similarly, VI (R = CH_3) absorbs at 1695 cm.$^{-1}$ (tertiary amide I band) and at 1655 cm.$^{-1}$ and 1625 cm.$^{-1}$ (primary amide I and II bands). In contrast, the spiroimidazolidone IV (R = CH_3) absorbs only at 1695 cm.$^{-1}$ and, as would be expected from its five-membered lactam structure,[9] it shows no bands in the amide II region.

While the above interconversions strongly indicated that the compounds obtained in our experiments with ethyl orthoformate were the desired spiroimidazolones it seemed of interest to investigate other synthetic pathways leading to these materials. Indeed, when 1-methylaminocyclohexanecarboxamide was treated with formamide,[10] 1-methyl-1,3-diazaspiro[4.5]dec-2-en-4-one, I (R = CH_3) could be isolated as the major reaction product. Furthermore, this compound was also formed in the base catalyzed reaction between 1-methylaminocyclohexanecarboxamide and ethyl oxalate. The pathway of this reaction—which had been expected to lead to a piperazinetrione[11]—probably involved as intermediate an α-aminooxalylcarboxamide which was dehydrated with concomitant loss of carbon dioxide.

Finally, when the ethyl orthoformate reaction was extended to the 2-amino-2-phenylbutyramides VII (R = H or CH_3) the expected imidazolones VIII and IX were formed. Their structures were proven by catalytic reduction to the known 5-ethyl-5-phenyl-4-imidazolidone X (R = H)[3,7,12] and its 1-methyl derivative X (R = CH_3).

As all experimental findings clearly supported the imidazolone structure for the materials obtained by us in the ethyl orthoformate–aminoamide reaction, it seemed of interest to elucidate

(7) R. B. Whalley, E. L. Anderson, F. DuGan, J. W. Wilson, and G. E. Ullyot, *J. Am. Chem. Soc.*, *77*, 745 (1955).

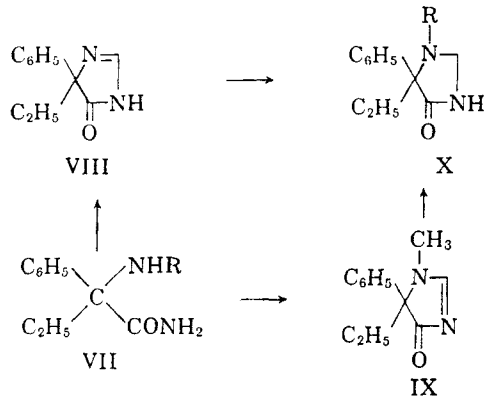
(8) H. Behringer and K. Schmeidl, *Chem. Ber.*, 90, 2510 (1957).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Wiley, New York, 1958, pp. 203–233.

(10) For a more detailed account of this reaction, see: E. Schipper, *Chem. & Ind.*, 464 (1960).

(11) S. R. Safir, J. J. Hlavka, and J. H. Williams, *J. Org. Chem.*, 18, 106 (1953).

(12) We are indebted to Dr. J. W. Wilson of Smith Kline & French Laboratories, Philadelphia, Pa., for supplying a number of samples for purposes of comparison.



the nature of Carrington's materials. When 1-formylaminocyclohexanecarboxamide (VI. R = H) was heated with acetic anhydride according to the directions of Carrington *et al.*,[3] the major reaction product consisted of a compound, m.p. 192–194° whose elementary analysis corresponded to that calculated for an acetyl derivative of the starting material. Inspection of its infrared spectrum revealed bands characteristic of the imide grouping (1742 cm.$^{-1}$ and 1680 cm.$^{-1}$)[9] and a peak at 1530 cm.$^{-1}$ corresponding to the NH deformation of a secondary amide; no band was observed in the 1650–1620 cm.$^{-1}$ region. The acetylation product thus must be represented by structure XI rather than by the alternate formulation VI (R = CO-CH_3). In none of our experiments were we able to repeat the preparation of Carrington's imidazolone, m.p. 90–92°. However, examination of the infrared spectra of crude acetylation mixtures always indicated the presence of a characteristic nitrile band at 2230 cm.$^{-1}$

When an authentic sample of the material[6] of m.p. 90–92° also was found to exhibit a strong nitrile peak, it became obvious that treatment of 1-formylaminocyclohexanecarboxamide (VI. R = H) with acetic anhydride had caused dehydration of the primary amide group leading to 1-formylaminocyclohexanecarbonitrile (XII). Hence, by analogy, Carrington's liquid "1-methyl-1,3-diazaspiro[4,5]dec-2-en-4-one" is the isomeric 1-(*N*-methyl - *N* - formyl)aminocyclohexanecarbonitrile (XIII).[13]

While, as above, acetic anhydride proved to be unsuitable for the dehydration of formylaminocyclohexanecarboxamides to spiroimidazolones, this conversion could be effected in the case of VI (R = CH_3), by employing as reagent a mixture of formic acid and formamide.

Discussion of spectral data. 1. Ultraviolet spectra. While *N*-substitution fixes the position of the azine linkage in 4(or 5) imidazolones, *N*-unsubstituted derivatives may conceivably exist in either the 4(5H)-imidazolone configuration (*A*) or as the tautomeric 5(4H)-imidazolone (*B*):

This problem had been investigated previously by Carrington *et al.*[3] who assigned the 5(4H)-imidazolone structure (*B*) to the 5,5-diphenyl-2-thiohydantoin reduction product of Biltz and Seydel.[14] The structural assignment was based on the fact that methylation of this reduction product yielded exclusively 1-methyl-4,4-diphenyl-5-imidazolone. Subsequently Edward and Martlew[15] pointed out that alkylation of amidine systems always was preceded by a tautomeric shift and that therefore the methylation results observed by Carrington *et al.*[3] were evidence that the unmethylated product possessed the 4(5H)-imidazolone structure (*A*). This reasoning was rejected by Carrington *et al.*[16] as not being applicable to acylamidine systems. Furthermore they elicited support for the 5(4H)-imidazolone structure by comparing the ultraviolet spectrum of 1,5-dimethyl-5-phenyl-4-imidazolone—which showed strong absorption at 270 mμ—with the spectra of the imidazolones obtained from the Raney nickel reductions of 5,5-diphenyl-2-thiohydantoin and 2-thio-1,3-diazaspiro[4.5]decanone-4, respectively. As these imidazolones exhibited end absorption only, their assignment to structural type *B* appeared justified.

In the light of our findings, however, the conclusions drawn by Carrington *et al.*[3,16] regarding the structure of these *N*-unsubstituted imidazolones are without basis of fact. In the first place, the diphenylimidazolone[12] of Biltz and Seydel[14] *does* absorb above 220 mμ (*vide infra*); secondly, Carrington's presumed spiroimidazolone—as was shown in the preceding section—appears to be 1-formylaminocyclohexanecarbonitrile (XII).

Inasmuch as we had at our disposal authentic samples of *N*-unsubstituted 4(5H)[or 5(4H)]imidazolones as well as *N*-substituted examples of structural type *A* and *B* it seemed of interest to investigate their spectral properties in the ultraviolet range. The results are shown in Table I.

The presence of two maxima in the spectrum of a neutral solution of the unsubstituted spiroimidazolone I or II (R = H) is somewhat unexpected. The peak at 256 mμ, its enhancement in basic solution and disappearance in acid parallels closely

(13) The nature of Carrington's "3-methyl-1,3-diazaspiro[4.5]dec-1-en-4-one" is not clear but since it was formed by methylation of XII (R = H) its identity with XIII is probable.

(14) H. Biltz and K. Seydel, *Ann.*, **391**, 215 (1912).

(15) J. T. Edward and E. F. Martlew, *Chem. & Ind.*, 193 (1954).

(16) H. C. Carrington, C. H. Vasey, and W. S. Waring, *Chem. & Ind.*, 377 (1954).

TABLE I

Compound	Ethanol		Alcoholic 0.1*N* KOH		Alcoholic 0.1*N* HCl	
	max (mμ)	log ε	max (mμ)	log ε	max (mμ)	log ε
I or II (R = H)	228	3.670	256	3.832	230	3.859
	256	3.159				
I (R = CH_3)	270	3.905	270	3.146	241	3.838
II (R = CH_3)	234	3.707	234	3.661	241	2.850

the spectral data reported by Kny and Witkop[17] for "4(5H)-imidazolone-5-acetic acid." Furthermore, neutral or basic solutions of compound VIII as well as of an authentic sample of Carrington's 5,5-diphenyl-4-imidazolone[3,12,14] showed maxima at 260 mμ and 265 mμ, respectively. While in neutral solution these materials exhibited end absorption only around 230 mμ, lowering of the *p*H effected the disappearance of the peaks in the 260 mμ region and gave rise to maxima at 235 mμ and 240 mμ, respectively. From these data it appears that in neutral or basic medium *N*-unsubstituted 4(5H)(or 5(4H))-imidazolones absorb generally in the 260 mμ region[18]; in turn, the peaks at 230–240 mμ seem to be specific for the absorption of the protonated compounds. The band at 270 mμ appears to be characteristic for 1-R-4(5H)-imidazolones and the position of the maximum probably is independent of ring substitution.[16]

The observed differences between the absorption spectra of 1-R-4(5H)- and 1-R-5(4H)-imidazolones readily permitted the structural assignment of II (R = $CH(OC_2H_5)_2$) to the product isolated from the reaction of 1-aminocyclohexanecarboxamide with an excess of ethyl orthoformate.

From the data presented in Table I it appears likely that in a polar solvent the *N*-unsubstituted spiroimidazolone behaves as a mixture of both possible forms I and II (R = H) and that ultraviolet spectroscopy cannot resolve the location of the double bond.

2. Infrared spectra. A number of significant differences existed between the infrared spectra of solid (potassium bromide pellets) 1-alkyl-4(5H)- and 1-alkyl-5(4H)-imidazolones. In the nonconjugated compounds (type *B*) the carbonyl absorption and the C=N stretching vibration occurred at 1740-1725 cm.$^{-1}$ and 1612-1609 cm.$^{-1}$, respectively. In the conjugated isomers (type *A*) these absorptions were shifted towards lower frequencies (1710-1695 cm.$^{-1}$ and 1550-1540 cm.$^{-1}$).

The diphenylimidazolone obtainable by ... duction of 5,5-diphenyl-2-thiohydantoin[3,14] exhibited peaks at 1725 cm.$^{-1}$ and 1600 cm.$^{-1}$ but did not absorb in the 1550-cm.$^{-1}$ region. Similar bands (1740 cm.$^{-1}$ and 1610 cm.$^{-1}$) were shown by the imidazolone formed in the reaction between ethyl orthoformate and 2-amino-2-phenylbutyramide. These compounds, therefore, belong to the class of 5(4H)-imidazolones, and the structure proposed by Carrington *et al.*[3] for the diphenylimidazolones of Biltz and Seydel[14] is thus substantiated. Furthermore, the 5(4H)-imidazolone structure could also be assigned on the basis of infrared data to the methiodide V, formed by methylation of 1-methyl-1,3-diazaspiro [4.5]dec-2-en-4-one, (I. R = CH_3).

In the case of our *N*-unsubstituted spiroimidazolone, the infrared spectrum surprisingly indicated that this material existed in its solid state (potassium bromide pellets) primarily in the 4(5H)-imidazolone form I (R = H) (maxima at 1710 cm.$^{-1}$ and 1540 cm.$^{-1}$). However, the infrared spectrum of a chloroform solution of this compound showed a striking hypsochromic shift to maxima characteristic of the nonconjugated structure II (R = H). As the spectra of chloroform solutions of the *N*-methyl derivatives I (R = CH_3) and II (R = CH_3) were practically identical with their corresponding spectra as solids, it appears likely that intermolecular hydrogen bonding[19] is responsible for the unexpected solid state spectrum of the *N*-unsubstituted spiro-imidazolone.

From these data, then, it can be deduced that the problem of the 4(5H)- *vs.* the 5(4H)-imidazolone structure of *N*-unsubstituted derivatives is generally resolvable in favor of the 5(4H)- configuration (type *B*), provided that solvent and association effects are considered.

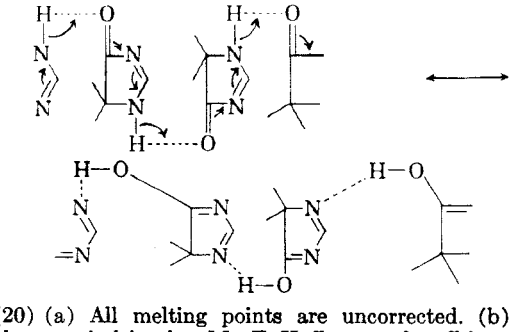
EXPERIMENTAL[20]

Aminonitriles. These compounds were prepared by a modified Strecker synthesis.[21] To a cooled and stirred solution containing 196 g. (2 moles) of cyclohexanone, 2 moles of an amine hydrochloride, 200 ml. of methanol, and 250 ml. of water was added a solution of 130 g. (2 moles) of potassium cyanide in 250 ml. of water. After the exothermic reaction had subsided, the reaction mixture was stirred for 24 hr. at room temperature and ultimately refluxed for 2 hr. The organic layer was separated and the aqueous layer was

(17) H. Kny and B. Witkop, *J. Am. Chem. Soc.*, **81**, 6245 (1959).

(18) A. Kjaer, *Acta Chem. Scand.*, **7**, 1017 (1953) reports an absorption maximum at 255 mμ for "2-benzyl-5(4H)-imidazolone."

(19) This association may be resonance-stabilized as follows:

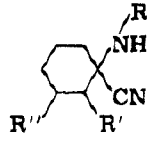


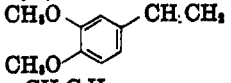
(20) (a) All melting points are uncorrected. (b) The authors are indebted to Mr. E. Hoffman and staff for microanalytical and spectral determinations.

(21) R. E. Steiger, *Org. Syntheses*, Coll. Vol. III, 88 (1955).

TABLE II

AMINOCYCLOHEXANECARBONITRILES

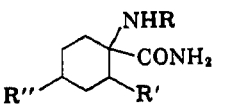


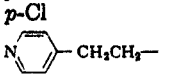
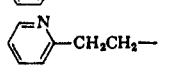
R	R′	R′	Emp. Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	M.P.	B.P.	Yield, %	Form
H	H	H		[a]								75	Base
CH_3	H	H	$C_8H_{15}N_2Cl$	55.00	54.78	8.66	8.86	16.04	16.05	113–114		90	Hydrochloride
C_2H_5	H	H	$C_9H_{17}N_2Cl$	57.46	57.24	9.06	9.01	14.92	14.75			74	Hydrochloride
$(C_2H_5)_2NCH_2CH_2$	H	H		[a]							120–130/7 mm.	80	Base
CH_2	CH_3	H	$C_9H_{16}N_2$	71.00	71.03	10.59	10.75	18.40	18.40		80–81/2 mm.	79	Base
CH_2	H	CH_3	$C_9H_{16}N_2$	71.00	70.87	10.59	10.63	18.40	18.22		84–87/3 mm.	96	Base
$C_6H_5CH_2$	H	H	$C_{14}H_{19}N_2Cl$	67.20	67.17	7.60	7.67	11.20	11.11	134–135		95	Hydrochloride
C_6H_5	H	H								74–76[b]		75	Base
	H	H	$C_{17}H_{24}N_2O_2$	70.80	70.67	8.39	8.16	9.71	9.70	97–99		45	Base
p-$CH_3C_6H_4$	H	H								77–78[c]		71	Base
p-$CH_3OC_6H_4$	H	H	$C_{15}H_{20}N_2O$	73.01	73.13	7.88	8.03	12.17	12.40	74–76		43	Base
o-$CH_3OC_6H_4$	H	H	$C_{15}H_{20}N_2O$	73.01	73.23	7.88	7.94	12.17	11.90	87–89		50	Base
p-ClC_6H_4	H	H	$C_{13}H_{17}N_2Cl$	66.62	66.31	6.44	6.48	11.94	12.04	115–116		40	Base

[a] Not obtained in pure state. [b] R. V. Walther and R. Hübner, *J. prakt. Chem.*, 93, 119 (1916). [c] R. L. Betts and S. P. G. Plant, *J. Chem. Soc.*, 2070 (1928).

TABLE III

AMINOCYCLOHEXANECARBOXAMIDES

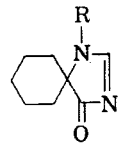


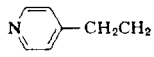
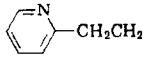
R	R′	R″	Emp. Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	M.P.	Yield,[a] %	Recrystn. Solvent
H	H	H	$C_7H_{14}N_2O$	59.12	59.40	9.92	9.75	19.70	19.81	105–106	60	Ether
CH_3	H	H	$C_8H_{16}N_2O$	61.50	61.62	10.32	10.36	17.93	18.15	137–138	89	Ether-ethanol 1:1
$C_6H_5CH_2$	H	H	$C_{14}H_{20}N_2O$	72.38	72.58	8.68	8.78	12.06	11.78	106–107	53	Heptane
$(C_2H_5)_2N(CH_2)_2$	H	H	$C_{12}H_{27}N_3O$	64.68	64.98	11.28	11.12	17.41	17.60	69–70	61	Pentane
CH_2	CH_3	H	$C_9H_{18}N_2O$	63.49	63.46	10.66	10.66	16.46	16.55	82–87	60	Hexane
CH_3	H	CH_3	$C_9H_{18}N_2O$	63.49	63.80	10.66	10.66	16.46	16.35	88–90[b]	5	Isooctane
CH_2	H	CH_2	$C_9H_{16}N_2O$	63.49	63.77	10.66	10.74	16.46	16.65	124–125[c]	26	Cyclohexane
C_2H_5	H	H	$C_9H_{18}N_2O$	63.49	63.82	10.66	10.92	16.46	16.40	63–65	69	Hexane
C_6H_5	H	H								148–149[d]	60	Ethyl acetate
p-$CH_3C_6H_4$	H	H	$C_{14}H_{20}N_2O_2$	67.71	67.45	8.12	8.35	11.28	11.35	125–126	40	Ether
o-$CH_3C_6H_4$	H	H	$C_{14}H_{20}N_2O_2$	67.71	67.55	8.12	8.21	11.28	11.20	157–158	16	Ethyl acetate
p-CH_3	H	H								155–156[d]	75	Methanol
p-Cl	H	H	$C_{13}H_{17}N_2OCl$	61.77	61.59	6.78	7.00	11.08	11.25	177–178	65	Benzene
	H	H	$C_{14}H_{21}N_3O$	67.98	68.01	8.56	8.66	16.99	17.25	155–156	40[e]	Ether
	H	H	$C_{14}H_{21}N_3O$	67.98	67.86	8.56	8.57	16.99	16.98	145–146	37[e]	Ethyl acetate

[a] Based on aminonitrile. [b] Isomer A. [c] Isomer B. [d] R. L. Betts and S. P. G. Plant, *J. Chem. Soc.*, 2070 (1928). [e] Based on 1-aminocyclohexanecarboxamide.

TABLE IV

1-R-1,3-DIAZASPIRO[4.5]DEC-2-EN-4-ONES



R	Emp. Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	M.P.	Yield, %	Recrystn. Solvent
CH_3	$C_9H_{14}N_2O$	65.03	65.17	8.49	8.32	16.85	16.61	120–121	77	Ethyl acetate
C_2H_5	$C_{10}H_{16}N_2O$	66.63	66.27	8.95	8.78	15.54	15.29	72–73	40	Ether
$(C_2H_5)_2N(CH_2)_2$	$C_{14}H_{25}N_3O$	66.89	67.04	10.03	10.32	16.72	16.42	78–79	30	Hexane
$C_6H_5CH_2$	$C_{15}H_{18}N_2O$	74.35	74.28	7.49	7.68	11.56	11.30	128–129	35	Ether
C_6H_5	$C_{14}H_{16}N_2O$	73.65	73.36	7.06	7.05	12.27	12.21	171–173	23	Ethyl acetate
p-$CH_3OC_6H_4$	$C_{15}H_{18}N_2O_2$	69.74	69.60	7.02	7.00	10.85	10.76	141–142	41	Ether
p-$CH_3C_6H_4$	$C_{15}H_{18}N_2O$	74.35	74.09	7.49	7.41	11.56	11.65	198–199	55	Ethyl acetate
	$C_{15}H_{19}N_3O$	70.00	70.01	7.44	7.54	16.33	16.60	143–144	70	Ethyl acetate
	$C_{15}H_{19}N_3O$	70.00	69.76	7.44	7.35	16.33	16.38	91–92	88	Ethyl acetate

extracted with several portions of chloroform. All organic layers were combined and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was either recrystallized from hydrocarbon solvents, distilled *in vacuo* or converted into a hydrochloride. A number of very unstable aminonitriles were converted directly and without prior purification to the corresponding aminoamides.

In addition to the aminocyclohexanecarbonitriles listed in Table II there were prepared by the above method 2-amino-2-phenylbutyronitrile and 2-methylamino-2-phenylbutyronitrile. No attempt was made to obtain these materials in pure form and the crude samples were hydrolyzed directly to the desired aminoamides.

Aminoamides. Arylaminocyclohexanecarboxamides were prepared according to the procedure of Betts *et al.*[5a] Alkyl-, aralkyl-, and aminoalkylcyclohexanecarboxamides were prepared by a modification of this procedure, in which the 48-hr. reaction time at room temperature was replaced by a 1-hr. heating period at 100°.[5b] Whenever the resulting aminoamides were water-soluble they were extracted with chloroform from their basic solutions. The extracts were dried, the solvent was removed *in vacuo* and the residual aminoamide recrystallized from the appropriate solvent.

The two β-pyridylethylaminocyclohexanecarboxamides were prepared according to the general procedure of Reich and Levine.[22] A mixture containing 14 g. of 1-aminocyclohexanecarboxamide, 10.8 g. of 2- or 4-vinylpyridine, 6 g. of glacial acetic acid, and 35 ml. of methanol was refluxed for 12 hr. The methanol was removed under reduced pressure and the residue was poured into an ice-water mixture. The solution was made strongly basic with 10% sodium hydroxide and the precipitate was collected by filtration, washed with water, dried, and recrystallized.

In addition to the aminocyclohexanecarboxamides listed in Table III the following aminobutyramides were prepared by the modified hydrolysis procedure.[5b]

2-Amino-2-phenylbutyramide (VII. R=H). The product was recrystallized from hexane-ethanol; yield, 26%, based on crude aminonitrile; m.p. 136–137°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.42; H, 7.79; N, 15.82.

2-Methylamino-2-phenylbutyramide (VII. R=CH_3). The compound was recrystallized from acetone-hexane; yield, 42% based on crude aminonitrile; m.p. 93–94°.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.85; H, 8.39; N, 14.30.

1-Aminocyclohexane-(N-methyl)carboxamide. The compound was prepared by the method of Frankel *et al.*[23]: 1-Aminocyclohexanecarboxylic acid hydrochloride[24] (33.4 g.) was dispersed in 300 ml. of acetyl chloride and 56 g. of phosphorus trichloride was added. The mixture was shaken in an ice bath for 20 min. and at 25° for 4 hr. After filtration 800 ml. of chloroform was added to the filtrate. The slurry was stirred and cooled in an ice bath while a solution of 35 g. of methylamine in 600 ml. of chloroform was added over a period of 1 hr. The reaction mixture was stirred at 25° for 12 hr. and refluxed for 2 hr. The solvent was removed by distillation and the residue was dissolved in 3*N* hydrochloric acid. The acid solution was washed with ether and then made alkaline with potassium hydroxide. The oil was extracted with ether. The extract was dried and distilled. The fraction, b.p./7 mm., 137–139°, was collected. It solidified spontaneously in the receiver and the solid was recrystallized from pentane; yield, 12 g. (40%), m.p. 61–62°.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.35; H, 10.10; N, 17.91.

4(5H)-Imidazolones. The compounds listed in Table IV were prepared by the following general procedure: A stirred solution consisting of a 1-R-aminocyclohexanecarboxamide and a 25-fold excess (by weight) of ethyl orthoformate was heated while the ethanol generated by the reaction was allowed to distill slowly over a 2-ft. Vigreux column. The reaction time varied from 1 to 5 days and the reaction was judged to be complete when a volume of alcohol exceeding the calculated amount by 20% had been collected. The excess orthoformate was removed under reduced pressure and the residual mass was recrystallized from an appropriate solvent.

1-Methyl-5-ethyl-5-phenyl-4-imidazolone (IX). The compound was obtained by applying the above procedure to 2-methylamino-2-phenylbutyramide (VII. R=CH_3). The solvent of recrystallization was ethyl acetate; yield, 55%, m.p. 172–174°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.48; H, 7.25; N, 13.70.

1-Methyl-1,3-diazaspiro[4.5]dec-2-en-4-one (I. R=CH_3). *a.* To a stirred and refluxing solution containing 15.6 g.

(22) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(23) M. Frankel, Y. Liwschitz, and A. Zilkha, *J. Am. Chem. Soc.*, **76**, 2814 (1954).

(24) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 3121 (1948).

of 1-methylaminocyclohexanecarboxamide, 14.6 g. of ethyl oxalate, and 75 ml. of absolute ethanol there was added in small portions 2.7 g. of sodium hydride. The suspension was refluxed for 30 min. and filtered. The filtrate was evaporated to dryness and the residue was taken up in 20 ml. of 2*N* hydrochloric acid. The insoluble portion was filtered and suspended in ethanol. The suspension was filtered and the filtrate was condensed to dryness. The residue (3 g.) after a recrystallization from ethyl acetate melted at 120–122°. Its identity with I (R = CH_3) was established by mixed melting point and infrared spectrum.

b. A solution containing 9 g. of VI (R = CH_3), 15 ml. of formic acid and 100 ml. of formamide was refluxed gently for 3 hr. Water (100 ml.) was added and the solution was extracted with chloroform. The extract was dried and the solvent was evaporated. The residue was recrystallized from ether and ethyl acetate; yield, 4.8 g. (60%); m.p. 120–121°.

c. A mixture consisting of 10 g. of 1-methylaminocyclohexanecarboxamide and 100 ml. of formamide was heated for 2 hr. at 180°. The solution was diluted with 100 ml. of water and extracted with chloroform. The extract was dried and the solvent removed by distillation. The residue was triturated with ether, the solid was filtered and recrystallized from ethyl acetate; yield, 3.5 g. (33%); m.p. 120–122°.

5(4H)-Imidazolones. 1,3-Diazaspiro[4.5]dec-1-en-4-one (II. R = H). A solution containing 20 g. of 1-aminocyclohexanecarboxamide and 100 g. of ethyl orthoformate was refluxed for 12 hr. The excess reagent was removed under reduced pressure and the residue was recrystallized from ethyl acetate; yield, 19.5 g. (91%); m.p. 165–166°.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.17; H, 7.82; N, 18.32.

The imidazolone could also be obtained by hydrolysis of the diethoxymethyl derivative II (R = $CH(OC_2H_5)_2$): Two grams of II (R = $CH(OC_2H_5)_2$) and 20 ml. of 2.5*N* hydrochloric acid were refluxed for 10 min. The solution was made basic with concentrated ammonium hydroxide and the volume was condensed to 10 ml. The solution was extracted with chloroform and the extract was dried. The solvent was evaporated and the residue was recrystallized from ethyl acetate to give 0.8 g. (67%) of II (R = H), m.p. 165–166°.

1-Diethoxymethyl-1,3-diazaspiro[4.5]dec-1-en-4-one [II. R = $CH(OC_2H_5)_2$]. 1-Aminocyclohexanecarboxamide (20 g.) was refluxed for 12 hr. with a 25-fold excess of ethyl orthoformate (500 g.). The product was recrystallized from pentane; yield: 33 g. (95%), m.p. 48–49°.

Anal. Calcd. for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.33; H, 8.96; N, 11.20.

When in the above reaction II (R = H) was employed as starting material in place of 1-aminocyclohexanecarboxamide, II (R = $CH(OC_2H_5)_2$) could be obtained in quantitative yield.

3-Methyl-1,3-diazaspiro[4.5dec-1-en-4-one (II. R = CH_3). A solution consisting of 2.7 g. of 1-aminocyclohexane-(*N*-methyl)carboxamide and 25 ml. of ethyl orthoformate was refluxed for 4 days. The excess reagent was distilled and the oily residue was dissolved in pentane. The solution was cooled to −10° and the material was collected by filtration and recrystallized from pentane; yield, 2.2 g. (76%); m.p. 51–52°.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.08; H, 8.27; N, 16.69.

4-Ethyl-4-phenyl-5-imidazolone (VIII). Twenty grams of 2-amino-2-phenylbutyramide (VII. R = H) and 200 ml. of ethyl orthoformate were refluxed for 24 hr. After removal of the excess reagent, the residue was recrystallized from ether; yield, 9.5 g. (45%), m.p. 111–112°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.19; H, 6.52; N, 14.80.

1,3-Dimethyl-1,3-diazaspiro[4.5]dec-1-en-4-one iodide (V). A mixture containing 4 g. of 1,3-diazaspiro[4.5]dec-1-en-4-one (II. R = H), 4 g. of silver oxide, and 40 ml. of methyl iodide was refluxed for 5 hr. The hot suspension was filtered and the filtrate was evaporated to dryness. The residue was triturated with ethyl acetate and the solid was collected by filtration. It was recrystallized from ethanol-ether; yield, 2.3 g. (34%); m.p. 190–192°.

Anal. Calcd. for $C_{10}H_{17}N_2OI$: C, 38.97; H, 5.56; N, 9.09. Found: C, 38.95; H, 5.78; N, 9.16.

1-Formylaminocyclohexanecarboxamide (VI. R = H). A solution of 3 g. of 1,3-diazaspiro[4.5]dec-1-en-4-one (II. R = H) in 30 ml. of water was refluxed for 2 hr. The solution was condensed to half volume, the solid was filtered and recrystallized from ethyl acetate; yield, 3 g. (88%), m.p. 174–175°. The material proved to be identical with Carrington's[3] alleged "2-hydroxy-1,3-diazaspiro[4.5]decanone-4."

1-(N-Methyl-N-formyl)aminocyclohexanecarboxamide (VI. R = CH_3). The preceding reaction conditions were applied to 5 g. of 1-methyl-1,3-diazaspiro[4.5]dec-2-en-4-one (I. R = CH_3). The material was recrystallized from ethyl acetate; yield, 4.5 g. (82%), m.p. 164–165° (reported[3] for "1-methyl - 2 - hydroxy - 1,3 - diazaspiro[4.5]decanone - 4," m.p. 160–161°).

1-Formylaminocyclohexane-(N-acetyl)carboxamide (XI). A solution containing 10 g. of VI (R = H) and 100 ml. of acetic anhydride was refluxed for 1 hr. and the excess of reagent was distilled under reduced pressure. The residual oil solidified on standing. The solid was triturated with ether, filtered and recrystallized from ethyl acetate; yield, 6 g. (48%), m.p. 192–194°.

Anal. Calcd. for $C_{10}H_{16}N_3O_2$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.45; H, 7.83; N, 13.08.

Careful examination of the mother liquors, including column chromatography (Florosil) did not reveal the presence of any other solid material.

1,3-Diazaspiro[4.5]decanone-4 (IV). A solution consisting of 10 g. of II (R = H) and 100 ml. of absolute ethanol was subjected to hydrogenation at an initial pressure of 45 lb.; palladium on charcoal (5%) was employed as catalyst. After completed reaction the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate; yield, 10.2 g. (99%); m.p. 158–159°. The material was identical with an authentic sample of IV.[3,6]

5-Ethyl-5-phenylimidazolidone-4 (X. R = H). When the preceding procedure was applied to 10 g. of VIII, the imidazolidone X was obtained in quantitative yield; m.p. 143–144° (reported[3] m.p. 142–143°).

1-Methyl-5-ethyl-5-phenylimidazolidone-4 (X. R = CH_3). When the imidazolone IX was subjected to the above catalytic hydrogenation, it was reduced in quantitative yield to compound X (R = CH_3), m.p. 154–155°. This material was identical (mixed melting point, infrared spectrum) with the product obtained in the reaction between 2-methylamino-2-phenylbutyramide and formamide.[10]

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