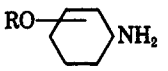
TABLE I

ALKOXYCYCLOHEXYLAMINES



R	Catalyst[a]	Time, hr.	Products, %[b] D	E	F	G	H
2-CH_3	A	31	7.5	57.0	33.0		2.5
2-CH_3[c]	A	4.5	10.25	77.25	10.0		2
3-CH_3[c]	A	3	5.5	70.0	24.5		
4-CH_3[c]	A	24	24.25	74.75	1.0		
2-C_2H_5	A	14	8	70[d]	9		10
3-C_2H_5	A	20	9	66[e]	25		
4-C_2H_5	A	8	30	56.5[f]	12		
2-C_3H_7	A	24	3	75–80	16		
3-C_3H_7	A	10	4	80[g]	15		
4-C_3H_7	A	6–7	16	79[h]	4.5		
2-C_4H_9	A	12	3.5	65	9		20
2-C_4H_9[c]	A	4		*i*			
4-C_4H_9	A	4	13.5	80	6.0		
2-CH_3	B	5.5	35.5	41.5	23.0		
3-CH_3	B	6–10	9.4	27.5	8.0	26.5	25.0
4-CH_3	B	6–10	19	54		9.0	17.0
2-C_2H_5	B	7	6	44		11.0	38.5
3-C_2H_5	B	3.5	26.5	20.5	6	37.0	10.0
4-C_2H_5	B	9	20	24	1.5	22.5	30.0
2-CH_3	C	48	3.5	60.0		4	33
3-CH_3	C	3.5	35.5	3		50	7
4-CH_3	C	8	2	61			37.0
2-C_2H_5	C	30	2	71			24.0
4-C_2H_5	C	15	7	46.5	25		20.5

[a] A = 5% rhodium on alumina in a 40% weight ratio of catalyst to alkoxyaniline, solvent was ethyl alcohol unless indicated; B = platinum oxide, 5% weight ratio; C = 5% palladium on carbon, 50% weight ratio. [b] Unless otherwise indicated, per cent composition was determined by g.l.c. D = cyclohexylamine, E = alkoxycyclohexylamine, F = alkoxyaniline, G = dicyclohexylamine, H = high boilers. The high-boiling components as seen from infrared examination were free of aromatic material and showed strong broad ether bands at 9.05 μ. They were assumed to be mixtures of mono- and dialkoxydicyclohexylamines with the latter in far greater amounts. [c] Reduction carried out in alcohol containing 1 equiv. of acetic acid. [d] A 59% yield was obtained on distillation, b.p. 180° (750 mm.), $n^{25}D$ 1.4529; see ref. 1. [e] A 58% yield on distillation, b.p. 194–197° (755 mm.); see ref. 1. [f] A 50% yield on distillation; same constants as in ref. 1. [g] A 60% yield on distillation, b.p. 105–110° (21 mm.), $n^{25}D$ 1.4608; see ref. 1. [h] A 68% yield on distillation, b.p. 115° (40 mm.), $n^{22}D$ 1.4588; see ref. 1. [i] Distilled yield, 61.5%.

4-Butoxycyclohexylamine.—A solution of 24.75 g. (0.15 mole) of 4-butoxyaniline in 150 ml. of absolute ethyl alcohol was hydrogenated in the presence of 10.0 g. of 5% rhodium on alumina under 3.5-atm. pressure at 60°. When uptake was complete, the solut on was filtered from the catalyst and a sample was subjected to gas–liquid chromatography.[7] The catalyst was washed thoroughly with more alcohol. The solution was then concentrated and the residue was distilled, b.p. 128–130° (32 mm.), $n^{25}D$ 1.4576, 70% yield.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.14; H,12.36; N, 8.18. Found: C, 70.28; H, 12.19; N, 8.28.

2-Propoxycyclohexylamine was similarly prepared in 62% yield, b.p. 205–208° (758 mm.), $n^{25}D$ 1.4541.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.73; H, 12.22; N, 8.90. Found: C, 68.74; H, 12.17; N, 9.13.

When 1 equiv. of acetic acid was used in the reductions the solution, after removal of catalyst, was treated with an equivalent amount of 40% aqueous sodium hydroxide before submitting a sample for chromatography.

Hydrogenation in acetic acid was carried out in a few instances with little or no change in the amounts of the products of reduction, or any improvement in the reaction rate over that in alcohol and acetic acid. The work-up is as described in the next paragraph.

Reductions with Platinum Oxide or 5% Palladium on Carbon.—These were carried out at 60° in acetic acid (150 ml.) and 0.15 mole of compound. After removal of catalyst the solutions were concentrated in the presence of water to prevent acetylation. The residues were dissolved in water and kept cold while basified with excess sodium hydroxide solution to prevent loss of cyclohexylamine. The solutions were extracted with ether. After drying the extract over anhydrous magnesium sulfate and removal of drying agent, the ether solution was submitted for chromatography.

Synthesis of Monoacyl Hydrazides

TITO RABINI AND GIULIO VITA

Carlo Erba, Therapeutic Research Institute, Milan, Italy

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The hydrazides of carboxylic acids are usually prepared[1] by treating hydrazine hydrate with an anhydride, chloride,[2] amide,[3] or ester[4] of the corresponding acid or by heating its hydrazonium salt.[5] A common disadvantage of these reactions in addition to the necessity of preparing and frequently separating the above-mentioned carboxylic acid derivatives, consists in the formation of polyacyl hydrazides and tetrazines as by-products, which makes laborious purifications and low yields often inevitable. While looking for a way to obtain only the monoacyl hydrazides by direct reaction between the acid and hydrazine hydrate, avoiding even the isolation of the hydrazonium salt, we observed that complete transformation of the starting reagents requires considerable time and high temperatures and we have noticed that both of these conditions cause formation of by-products.

We have found, however, that activated alumina shows a remarkable catalytic activity, promoting the formation of the monoacyl hydrazides exclusively. Further, the catalyst permits the lowering of the reaction temperatures to the point that by-products are no longer formed. The water produced during the reaction must be continuously drawn off, *e.g.*, by azeotropic distillation.

(6) Since there did not appear to be any difference in activity between rhodium on alumina and rhodium on carbon in several comparative runs, the former was chosen because it was less of a fire hazard. All the noble metal catalysts used in this study were purchased from Engelhard Industries, Newark, N. J.

(7) The following conditions for g.l.c. analysis (by one of us, P.F.H.) were used: instrument, Burkell unit, Model K-2; column, 2-m. silicone L-46, 20% on acid-washed Chromosorb W, 80–100 mesh; carrier, helium 60 cc./min.; programmed (nonlinear) temperature at 170–230°. Known standards were used except for high-boiling materials.

(1) A. W. Johnson, C. E. Dalgliesh, and J. Walker, "Chemistry of Carbon Compounds," Vol. I, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1951, p. 600.

(2) C. Naegeli and G. Stefanovitsch, *Helv. Chim. Acta*, **11**, 636 (1928).

(3) H. M. Stanley, British Patent 785,346 (1957).

(4) L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1956, pp. 179, 213; H. Henecka and P. Kurtz, "Methoden der Organischen Chemie" (Houben–Weyl), Vol. VIII, Georg Thieme Verlag, Stuttgart, 1952, p. 676; Th. Curtius, *J. prakt. Chem.*, [2] **50**, 275 (1894); Th. Curtius, G. Schöfer, and N. Schwan, *ibid.*, [2] **51**, 185 (1895); Th. Curtius and E. Boetzelen, *ibid.*, [2] **64**, 314 (1901); R. Stollé, *ibid.*, [2] **69**, 145, 154, 486, 497 (1904); Th. Curtius and Melsbach, *ibid.*, [2] **81**, 548 (1910).

(5) Th. Curtius and H. Franzen, *Ber.*, **35**, 3239 (1902).

TABLE I

CATALYZED SYNTHESIS OF MONOACYL HYDRAZIDES[a]

Acid	Ml. of solvents/mole of acid: 1-Butanol	Benzene	Toluene	Temp., °C.	Time, hr.	Yield, %	Recovered unreacted salt, %	By-products, %
Acetic	100	55		96–101	2	80	2.55	0
Acetic	100	80		94–95	2.25	94	1	0
Isobutyric	100	40		115–116	8	95	2.8	0
Isobutyric	100	127		94–95	2.5	82	13	0
Phenylacetic	100	110		94–95	5	99	0	0
α-Crotonic	100	120		94–95	9	83	6	0
Glycine	100	Var.		94–110	24	0	...	...
Tosylglycine	1400	1680		94–95	12	88	...	1.55
Benzoic	100		80	115–117	6.25	93.3	2.18	0
o-Hydroxybenzoic	100		50	120–125	24	0	...	...
p-Hydroxybenzoic	100		50	120–125	24	0	...	...
p-Methoxybenzoic	100		95	115–116	12	80	14.2	3.1
p-Chlorobenzoic	190	240		94–95	18.5	84.9	15	0
Isonicotinic	130		60	115–117	12	94	1.4	2.3
Isonicotinic	120		70	109–110	11.75	90	7.1	0

[a] In the reported reactions 1.2 moles of hydrazine hydrate was used per mole of the acid. The amount of activated alumina (Alcoa F-1, from Aluminum Co. of America) was 20 g./mole of the acid.

TABLE II

UNCATALYZED SYNTHESIS OF MONOACYL HYDRAZIDES

Acid	Ml. of solvents/mole of acid: 1-Butanol	Benzene	Toluene	Temp., °C.	Time, hr.	Yield, %	Recovered unreacted salt, %	By-products, %
Isobutyric	100	45		115–116	8	81.8	10.5	0
Isobutyric	100	95		94–95	2.50	24	71	0
Phenylacetic	100	110		94–95	5	64	33.1	0
Benzoic	100		80	115–117	6.25	29	70.7	0
Isonicotinic				115–117	12	40	...	1.5
Isonicotinic				109–110	12	25	...	1.2

We noticed that the new method can be applied to a wide variety of aliphatic, aromatic, and heterocyclic acids, and some of their substituted derivatives. No advantage could be observed, however, when the substituent was an amino or hydroxyl group unless they were blocked, *e.g.*, by tosylation or alkylation, in which case reaction proceeds smoothly again.

A convenient way to carry out the reaction is to heat the solution of the acid in *n*-butyl alcohol with a slight excess of hydrazine hydrate in the presence of activated alumina, while the suspension is stirred rapidly. The water which is formed during the reaction is removed by azeotropic distillation with the continuously recycling alcohol, *e.g.*, by a Dean–Stark apparatus.[6] The gradual addition of a solvent of low dielectric constant like benzene or toluene further accelerated the reaction, maintaining the reaction temperature at the desired level. Table I gives the data related to some typical experiments. The reaction is completed, depending on the acid used, in times of 2 to 12 hr. in yields of 80–99%. Yields are given for monoacyl hydrazides as determined by potentiometric titration. Crystallized samples were checked by microanalysis and thin layer chromatography.

In Table II data related to some uncatalyzed reaction are summarized. The course of the reaction was checked by potentiometric titration: samples were taken at regular intervals from the solution which was separated from the alumina by simple decantation. The solvent of the samples was evaporated and the residue was dissolved in water.

In the titration with potassium hydroxide (Figure 1) a sharp step marks the point of equivalence of the hydrazonium salt; in the differential potentiometric titration with hydrochloric acid (Figure 2), the first peak corresponds to the hydrazine hydrate in excess and the second to the sum of the acid hydrazide and the hydrazonium salt. This simple analytical method is an exact and rapid tool to follow the reaction by giving the percentage of the various components in the reaction system, *i.e.*, the quantity of the unreacted and the end product independently of the hydrazine hydrate in excess.

(6) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 420.

Experimental

Phenylacetic Acid Hydrazide.—A 500-ml. four-necked flask was equipped with a mechanical stirrer, a dropping funnel, a thermometer, and a Dean–Stark apparatus.[6] Phenylacetic acid (136.15 g., 1.0 mole) was placed in the flask followed by 100 ml. of 1-butanol, 70 ml. (1.4 moles) of hydrazine hydrate, and 20 g. of activated alumina (Alcoa F-1 100–150 mesh). The flask was heated under vigorous stirring in an oil bath maintained at 140–150°; when the temperature of the reaction mixture reached 94–95° benzene was added gradually in order to obtain a heavy reflux. Water separated in the Dean–Stark apparatus and could be discharged for control. During the reaction the temperature tended to rise slowly but small additions of benzene were sufficient to maintain 94–95°. After 5 hr. the hot mixture was filtered, the alumina was washed with four 100-ml. portions of hot 1-butanol, and the filtrate was evaporated under reduced pressure to dryness; 150 g. (99%) of phenylacetic acid hydrazide was obtained, m.p. 118–120° uncor. Potentiometric titration proved in this case the absence of hydrazonium salt.

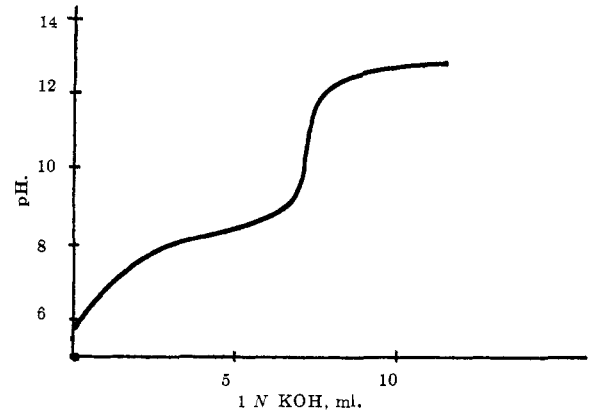


Figure 1.

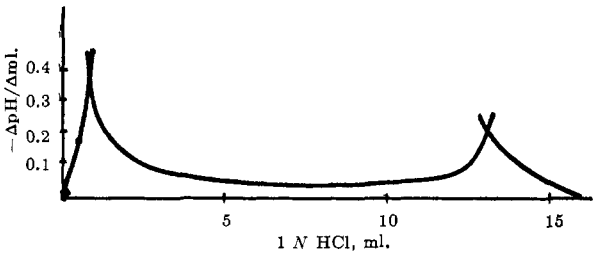


Figure 2.

The hydrazide was crystallized from ethanol.

Anal. Calcd.: C, 63.98; H, 6.71; N, 18.66; O, 10.65. Found: C, 64.10; H, 6.75; N, 18.47; O, 10.58.

Thin layer chromatography on silica gel with various solvents showed one spot.

Acknowledgment.—The authors are indebted to Dr. G. Tosolini for chromatography and to Mr. G. E. Gradogna for technical collaboration.

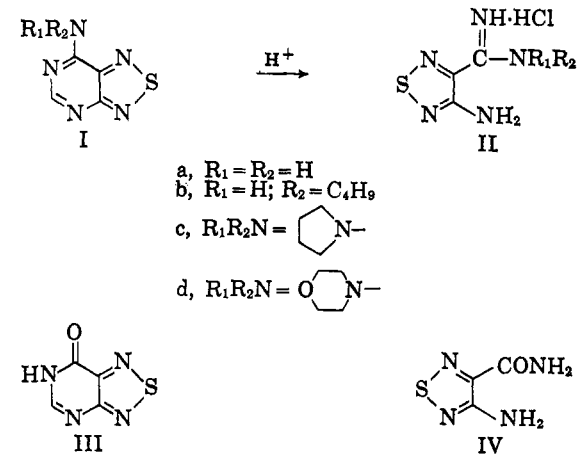
Acidic Cleavage of Amino[1,2,5]thiadiazolo[3,4-*d*]- and -*v*-triazolo[4,5-*d*]pyrimidines to 1,2,5-Thiadiazole-[1] and *v*-Triazolecarboxamidines[2]

Y. FULMER SHEALY AND C. ALLEN O'DELL

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama

Received February 19, 1965

The pyrimidine ring of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ia) has been opened by aqueous base and by primary amines, the latter agents producing N-alkyl carboxamidines.[3] During studies on possible modes of ring cleavage, 7-pyrrolidino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ic) was treated with dilute hydrochloric acid in dioxane at 85°. The product had the composition of the hydrochloride of the amino carboxamidine IIc, and the ultraviolet absorption properties were consistent with this structure. In order to gain additional support for the formation of this type of product, 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (Ib) was cleaved under the same conditions to the known[3] 4-amino-N-butyl-1,2,5-thiadiazole-3-carboxamidine (IIb). This reaction occurred much more rapidly than the formation of IIb in the reaction of Ia with butylamine, a reaction that evidently proceeds *via* the 7-butylamino derivative (Ib).[3] The acidic cleavage reaction was also successfully applied to the 7-amino (Ia) and the 7-morpholino (Id) derivatives; however, the yield of the amidine (IId) from the 7-morpholino derivative was lowered by a competing hydrolytic reaction that produced [1,2,5]thiadiazolo[3,4-*d*]pyrimidin-7(6H)-one (III) and 4-amino-1,2,5-thiadiazole-3-carboxamide (IV). Examination of aliquots from such a reaction by thin layer chromatography indicated that IId and III were formed simultaneously and that IV was then formed from III. The yields of the carboxamidines, with the exception of IId, were 68–82%. Further confirmation of the aminocarboxamidine structures was obtained by recyclizing 4-amino-1,2,5-thiadiazole-3-carboxamidine (IIa) to the thiadiazolopyrimidine (Ia) with ethyl orthoformate. In addition, alkaline hydrolysis of IIc gave 4-amino-1,2,5-thiadiazole-3-carboxylic acid.



Acidic cleavage of the thiadiazolopyrimidines (I) appears to be less complicated than acidic degradation of certain related heterocycles. Although the formation of III and IV, in addition to IId, from the 7-morpholino derivative is reminiscent of the acidic hydrolysis of 4-aminopteridine to 4(3H)-pteridinone and further degradation products,[4] the derivative (Ia) comparable to 4-aminopteridine gave a high yield of the amidine (IIa). Adenine, the purine analog of Ia, has been degraded under acidic conditions to glycine and ammonia,[5,6] and heating adenine at 150° for 2 hr. with 6 *N* hydrochloric acid gave only a 10% yield of 5-(or 4-) aminoimidazole-4- (or 5-) carboxamidine.[5,7]

(1) Part V on Thiadiazoles. Part IV: Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **29**, 2141 (1964).

(2) This investigation was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(3) Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, **29**, 2135 (1964).

(4) A. Albert, D. J. Brown, and G. Cheesman, *J. Chem. Soc.*, 474 (1951).

(5) L. F. Cavalieri, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **71**, 3973 (1949).

(6) R. H. Lindsay, W. K. Paik, and P. P. Cohen, *Biochem. Biophys. Acta*, **58**, 585 (1962).

(7) However, substituents on the adjacent ring-nitrogen atom facilitate this cleavage; 1-methyladenine and adenine N-oxide were cleaved by hydrochloric acid under milder conditions to 5- (or 4-) amino-N-methylimidazole-4- (or 5-) carboxamidine[8] and to 5- (or 4-) aminoimidazole-4- (or 5-) carboxamidoxime,[9] respectively. Similarly, 7-amino-*v*-triazolo[4,5-*d*]pyrimidine N-oxide (6-oxide of Va) was easily cleaved to the corresponding *v*-triazolecarboxamidoxime (VI, R_1 = H; R_2 = OH) by concentrated hydrochloric acid.[10]

(8) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(9) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).

(10) M. A. Stevens, H. W. Smith, and G. B. Brown, *ibid.*, **82**, 3189 (1960).