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No. 08-034065- -00007-0000

Fecha: 2012-07-06 16:47:07

Tra. 11 PATENTE IYII

Act. 523 RESPUESTA

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 7

Referencia: Expediente No. 08.034.065

Solicitud de Patente de Invención titulada: "Derivados plaguicidas de fenilamina sustituida con tiazoliloxi"

Solicitante: Bayer CropScience AG.

RESPUESTA AL OFICIO NOTIFICADO POR FIJACIÓN EN LISTA

DEL 11 DE ABRIL DE 2012, OFICIO NO. 05595 (ART 46 BUSQUEDA DE ANTERIORIDADES)

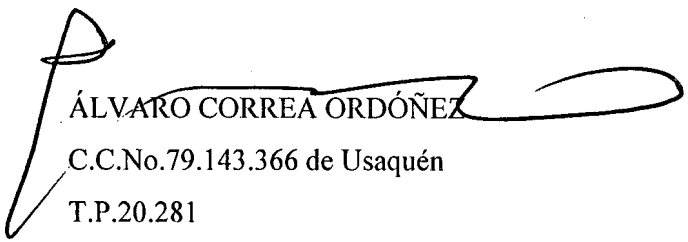
ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al oficio emanado por ese Despacho dentro del término legal:

1. Presento copia completa del siguiente documento:

Taylor E C ET AL: "A Convenient Synthesis of N, N'-Disubstituted Formamidines and Acetamidines". Journal of Organic Chemistry, Vol 28., pages 1108-1112.

En virtud de lo anterior, solicito que se proceda con el análisis de patentabilidad para la invención que se tramita en este expediente.

Atentamente,


ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexo: Copia del documento Taylor E C ET AL.

MGT/BOGDMS-#1133733-V1-P2008_000010.DOC

A Convenient Synthesis of *N,N'*-Disubstituted Formamidines and Acetamidines¹EDWARD C. TAYLOR AND WENDELL A. EHRHART²

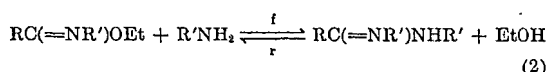
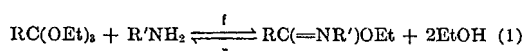
Frick Chemical Laboratory, Princeton University, Princeton, New Jersey

Received November 15, 1962

The reaction of ethyl orthoformate with alkylamines in the presence of acetic acid has been shown to lead to *N,N'*-dialkylformamidines in good yield. Under similar conditions ethyl orthoacetate gives *N,N'*-dialkylacetamidines. Reaction of ethyl orthoacetate with one mole of an aromatic amine, preferably in the presence of acetic acid, gives an ethyl *N*-arylacetimidate, while reaction with two moles of an aromatic amine in the presence of acetic acid gives an *N,N'*-diarylacetamidine. The role of the acetic acid in these reactions is discussed.

We have recently described¹ a convenient synthesis of formamidine acetate by the reaction of ethyl orthoformate with ammonia in the presence of acetic acid. The present paper describes an extension of this reaction to the synthesis of *N,N'*-disubstituted formamidines and acetamidines from the reaction of aliphatic amines with ethyl orthoformate and ethyl orthoacetate, respectively.

The reaction of ethyl orthoformate with aromatic primary amines has been studied extensively,⁴⁻⁹ primarily in recent years by Roberts,¹⁰⁻¹³ who has advanced convincing evidence to show that the course of the interaction of aromatic amines, ortho esters, formamidines, and formimidates is highly dependent on acid catalysis. The principal reactions involved are summarized in equations 1 and 2 (below). Reactions 1f and 2f are not



highly dependent on acid catalysis, since they proceed rapidly in the absence of acid. Reaction 2f is apparently much faster than 1f since, in the absence of acid, aromatic amines react with even a large excess of ethyl orthoformate to give the amidine only. Reaction 2r, on the other hand, is highly dependent on acid catalysis and explains the formation of imido ester when small amounts of acid are present in equal molar mixtures of aromatic amines and ethyl orthoformate. The amidine is thought to form rapidly *via* reactions 1f and 2f and then gradually to revert to imido ester *via* reaction 2r, presumably until an equilibrium position is reached. When two moles of aromatic amine are present per mole of ortho ester, amidine is obtained whether acid is present or not. It thus appears that in the absence of acid the product of kinetic control is obtained, since for all practical purposes reaction 2 is irreversible under

these conditions. In the presence of acid, on the other hand, reaction 2 becomes readily reversible and thus the product of thermodynamic control is formed.

We have investigated the reaction of ethyl orthoformate with various *aliphatic* amines, as well as the effect of acid on the course of the above equilibria reactions.¹⁴ Table I summarizes our results. It is interesting to point out that heating a mixture of two moles of cyclohexylamine with one mole of ethyl orthoformate for 1.5 hours at 130–140° gave *N,N'*-dicyclohexylformamidine in only 2.1% yield. When the reaction mixture was heated for 94 hours, the product was obtained in only 15% yield. By contrast, however, when two moles of cyclohexylamine were added to an equimolar mixture of ethyl orthoformate and glacial acetic acid and the reaction mixture heated for 1.25 hours, *N,N'*-dicyclohexylformamidine acetate was formed in 85% yield. The effect of acid on the course of amidine formation is thus dramatically illustrated. A number of other symmetrical *N,N'*-dialkylformamidines have been prepared by the above method in yields ranging from 55 to 85% and are summarized in Table I.

TABLE I
N,N'-DISUBSTITUTED FORMAMIDINES FROM ETHYL ORTHOFORMATE

Amine	Mole ratio of amine to EOF	Mole ratio of HOAc to EOF	Time, hr.	Product	Yield, %
$\text{C}_6\text{H}_{11}\text{NH}_2$	2	1	1.25	$\text{HC(=NC}_6\text{H}_{11}\text{)-NHC}_6\text{H}_{11}$	85 ^b
	2	1/12	1.5		41 ^a
	2	1/12	4.5		42 ^a
	1	1/12	1.5		49 ^a
	2	0	94		15 ^c
	2	0	1.5		2.1 ^c
$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$	2	1	2	$\text{HC(=NCH}_2\text{C}_6\text{H}_5\text{)-NHCH}_2\text{C}_6\text{H}_5$	68 ^c
$n\text{-C}_4\text{H}_9\text{NH}_2$	2	1	2	$\text{HC(=NC}_4\text{H}_9\text{-}n\text{)-NHC}_4\text{H}_9\text{-}n$	55 ^c
$n\text{-C}_2\text{H}_5\text{NH}_2$	2	1	1.5	$\text{HC(=NC}_2\text{H}_5\text{-}n\text{)-NHC}_2\text{H}_5\text{-}n$	62 ^b
CH_3NH_2	2	1	1.1	$\text{HC(=NCH}_3\text{)-NHCH}_3$	80 ^a

^a Isolated as the picrate. ^b Isolated as the acetate by distillation. ^c Isolated as the free amidine.

Table I also summarizes attempts to prepare *N,N'*-dicyclohexylformamidine by the reaction of ethyl orthoformate with cyclohexylamine in the presence of small quantities of acetic acid rather than one mole. Al-

(14) In spite of the extensive work carried out previously on the reaction of ethyl orthoformate with aromatic amines, no reference could be uncovered dealing with the reaction of this reagent with aliphatic amines.

(1) This work was supported in part by a research grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Parke, Davis and Co. Fellow in Chemistry, 1958–1959.

(3) E. C. Taylor and W. E. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

(4) L. Claisen, *Ann.*, **287**, 360 (1895).

(5) R. Walther, *J. prakt. Chem.*, **52**, 429 (1895); **53**, 472 (1896).

(6) C. Goldschmidt, D.R. Patent 97103 (1898); D.R. Patent 103982 (1899); *Chem. Ztg.*, **22**, 1033 (1898); **26**, 743 (1902); *J. Chem. Soc.*, **82**, 785 (1902).

(7) F. B. Dains and E. W. Brown, *J. Am. Chem. Soc.*, **31**, 1148 (1909).

(8) F. B. Dains, O. O. Malleis, and J. T. Meyers, *ibid.*, **35**, 970 (1913).

(9) Y. Mizuno and M. Nishimura, *J. Pharm. Soc. Japan*, **68**, 58 (1948); *Chem. Abstr.*, **44**, 331 (1950).

(10) R. M. Roberts, *J. Am. Chem. Soc.*, **71**, 3848 (1949).

(11) R. M. Roberts, *ibid.*, **72**, 3603 (1950).

(12) R. M. Roberts, R. H. DeWolfe, and J. H. Ross, *ibid.*, **73**, 2277 (1951).

(13) R. M. Roberts and R. H. DeWolfe, *ibid.*, **76**, 2411 (1954).

though the desired amidine was obtained in each case, it is clear that the use of a full mole of acetic acid is beneficial. It is also noteworthy that small differences in isolation technique, such as the height of the distilling head used in the removal of ethanol formed in the reaction, apparently play an important part in determining the yield of amidine obtained from those reaction mixtures which contained either no acid or only small amounts of acid. It appears that under these conditions a high percentage of the amidine formation takes place during the distillation by displacement of reaction 2 to the right by removal of ethanol.

Attempts to prepare formimidic esters by the reaction of ethyl orthoformate with aliphatic amines failed. In fact, a better yield of *N,N'*-dicyclohexylformamidine was obtained when equimolar amounts of the amine and ortho ester were heated in the presence of a little acetic acid (conditions which give imido esters when aromatic amines are used) than when two molecular proportions of the amine were used (conditions which give amidines with aromatic amines). If we make the reasonable assumption that equations 1 and 2 (p. 1108) correctly describe the reactions of aliphatic amines as well as aromatic amines¹³ with ethyl orthoformate, then the above observations can be interpreted as follows. The equilibrium position for the reaction of an aliphatic amine with ethyl orthoformate is probably in favor of the starting materials, so that acetic acid, in addition to catalyzing the reaction, also removes amidine from the equilibrium by salt formation, thus displacing reaction 2 to the right. The fact that reasonable yields of amidine can be obtained when only small amounts of acid are used can be rationalized on the assumption that most of the reaction leading to amidine occurs during work-up when ethanol is removed by distillation. The fact that formimidic esters have not been observed in the reaction of ethyl orthoformate with aliphatic amines probably indicates that these materials are unstable under the reaction conditions and are rapidly decomposed by reactions 1r and/or 2f.

Two methods have previously been available for the preparation of symmetrical *N,N'*-dialkylformamidines. Pinner¹⁵ and others¹⁶ have prepared a large number of these materials as their hydrochlorides by reaction of aliphatic amines with ethyl formimidate, prepared from hydrogen cyanide and ethanol. This procedure requires several days and elaborate precautions for the exclusion of moisture. Grundmann and Kreutzberger¹⁷ have recently described an alternative method for the preparation of *N,N'*-dialkylformamidines by the reaction of aliphatic amines with *s*-triazine. Although this procedure is simple and gives excellent yields, *s*-triazine is a difficultly available intermediate. The method described in the present paper would seem to compare favorably with the above methods for the laboratory preparation of *N,N'*-dialkylformamidines.

The above reaction has been extended to the preparation of *N,N'*-disubstituted acetamidines by the reaction of aliphatic primary amines with ethyl orthoacetate. The only previous examples of this reaction appear to

have been carried out by Rockwell¹⁸ and were reported in an unpublished doctoral thesis. He examined the reaction of some twenty primary amines (aliphatic and aromatic) with ethyl orthoacetate, and found that with about half of the amines employed the reaction stopped at the imido ester stage and further reaction to the amidine could not be effected even under severe conditions. In general, good yields of either an *N,N'*-disubstituted acetamidine or the corresponding imido ester were obtained, and in only one instance (with β -naphthylamine) were both products isolated from the same reaction. It appears that no attempt was made to isolate imido esters from reactions which gave satisfactory yields of amidine. The conclusion was reached¹⁸ that aromatic amines with electron-withdrawing groups or with ortho substituents yielded imido esters, and that aromatic amines with electron-donating groups or aliphatic amines yielded amidines.

We have reinvestigated the action of ethyl orthoacetate with a number of aliphatic and aromatic primary amines both in the presence and in the absence of acetic acid. The results are tabulated in Table II. As

TABLE II
REACTION OF AMINES WITH ETHYL ORTHOACETATE

Amine	Mole ratio of amine to EOA	Mole ratio of HOAc to EOA	Time, hr.	Amidine, %	Yield of ethyl acetimidate, %
$C_6H_{11}NH_2$	2	1	1.5	91 ^b	
	2	1/12	1.5	66 ^a	
	1	1/12	2.5	60 ^a	
	2	0	94	31 ^a	
	2	0	1.5	0.5 ^a	
$C_6H_5CH_2NH_2$	2	1	1	73 ^c	
	2	0	7	41 ^c	
$H_2NCH_2CH_2NH_2$	1	1	0.5	85 ^{b,d}	
	1	0	94	67 ^{e,d}	
$C_6H_5NH_2$	2	1/12	2	76 ^c	
	1	1/24	1.5	5.2 ^c	88
	2	0	1.5	Trace	69
	2	0	4	4.6 ^c	
	1	0	1.5	Trace	59
$o\text{-CH}_3OC_6H_4NH_2$	2	1	1.3	72 ^c	
	2	1/12	1.75	50 ^c	
	1	1/12	1.5	1.7 ^c	87
	0.66	0	5		90 ^f
	2	0	1.5		59
$o\text{-CH}_3C_6H_4NH_2$	2	1	1.5	57 ^c	
$o\text{-ClC}_6H_4NH_2$	2	2/3	1.5	30 ^c	
$p\text{-NO}_2C_6H_4NH_2$	2 ^g	1	1.25	25 ^c	
	2 ^g	0	1.25		Trace

^a Isolated as the picrate. ^b Isolated as the acetate. ^c Isolated as the free amidine. ^d 2-Methyl- Δ^2 -imidazoline. ^e Rockwell (ref. 18) reported an 83% yield of the amidine under these conditions. ^f This experiment was a repetition and confirmation of an experiment carried out by Rockwell (ref. 18). ^g One mole of pyridine was added.

expected on the basis of the reactions reported above between ethyl orthoformate and amines, it was found that amidine formation proceeded faster and in higher yield in the presence of acetic acid. In fact, under these conditions, it was found possible to prepare several acetamidines from aromatic amines having electron-withdrawing groups and/or *ortho* substituents, in

(15) A. Pinner, *Ber.*, **16**, 352, 1643 (1883).

(16) "The Chemistry of Penicillin," ed. by H. T. Clarke, J. R. Johnson, and Sir Robert Robinson, Princeton University Press, Princeton, N. J., 1949, p. 815.

(17) C. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955).

(18) D. M. Rockwell, doctoral dissertation, Yale University, 1931.

contrast to the results obtained by Rockwell. In general, the difference between the reactions of aromatic amines with electron-donating groups and those with electron-withdrawing groups is not so pronounced as Rockwell's results indicated. It would, in fact, appear that this author may have had traces of acid in his reaction mixtures in certain cases. For example, it was reported that an excellent yield of *N,N'*-diphenylacetamide was obtained by heating two moles of aniline with one mole of ethyl orthoacetate for four hours. We have repeated this reaction and obtained the amidine in only 4.6% yield, along with a large amount of ethyl *N*-phenylacetimidate. However, addition of a small amount of acetic acid resulted in rapid formation of the amidine in 76% yield. When ethyl *N*-phenylacetimidate was heated with one mole of aniline, formation of the amidine was very slow unless acetic acid was added. This result is in contrast to the report of Lander¹⁹ that ethyl *N*-phenylacetimidate, prepared by another method, could be converted to *N,N'*-diphenylacetamide in good yield by heating with aniline for five hours. It would seem that traces of acid may have been present in this reaction mixture as well.

Ethyl *N*-*o*-methoxyphenylacetimidate was also readily converted to the amidine by heating with *o*-anisidine in the presence of acetic acid.

The above results suggest that with aromatic amines reaction with ethyl orthoacetate can be controlled in most instances to give either amidine or imido ester depending upon reaction conditions. To prepare the imido ester one heats an equimolar mixture of the aromatic amine and ethyl orthoacetate for a short time in the absence of, or better, in the presence of a small amount of acid. To prepare the amidine one heats a mixture of two moles of aromatic amine and one mole of ethyl orthoacetate in the presence of acid. With aliphatic amines we have not been able to prepare imido esters from ethyl orthoacetate. The formation of amidine is, however, aided by the addition of acid as is the case with aromatic amines.

While the reactions of ethyl orthoacetate with aliphatic amines appear to be qualitatively quite analogous to the reactions of ethyl orthoformate with these same amines, the reactions of this ortho ester with aromatic amines are significantly different from those of the orthoformate. Reaction 1f (p. 1108) must be rapid and not highly dependent on acid catalysis as it is with ethyl orthoformate. Reaction 2f, however, is slow and highly dependent on acid catalysis in marked contrast to the orthoformate case. Thus it is not necessary to invoke reaction 2r to explain imidic ester formation in the orthoacetate series although this path could account for some percentage of the product when acid catalysis is employed.

The effect of acids other than acetic acid for the catalysis of amidine formation has not been investigated, but Roberts¹⁰⁻¹² used a number of different acids successfully to catalyze reactions of aromatic amines with ethyl orthoformate. Acetic acid (and presumably other fatty acids) has the advantage that its amine salts are generally soluble in the reaction medium and that the resulting amidine salts are generally less hygroscopic than those derived from mineral acids.

(19) G. D. Lander, *J. Chem. Soc.*, 77, 729 (1900).

Symmetrical *N,N'*-diarylacetamidines have generally been prepared by the reaction of acetanilide or substituted acetanilides with phosphorus pentachloride to give an imido chloride, followed by reaction with appropriate amines.²⁰⁻²² Since the acetanilide is prepared by acetylation of the corresponding aromatic amine, the procedure described in the present paper consisting of the reaction of an amine with ethyl orthoacetate allows the preparation of amidine in one rather than in two steps. This latter procedure may also be advantageous in cases where phosphorus pentachloride reacts with other substituents in the molecule. It suffers from the disadvantage that ethyl orthoacetate is expensive and that only poor yields have thus far been obtained from aromatic amines carrying electron-withdrawing groups. The only method previously available for the preparation of *N,N'*-dialkylacetamidines has been the reaction of ethyl acetimidate hydrochloride with amines.²³ Although the use of ethyl orthoacetate is more expensive, the reaction requires much less time, no precautions need be taken for the exclusion of moisture, and the amidine is readily obtained as the slightly hygroscopic acetate rather than as a highly deliquescent hydrochloride.

Since the completion of this work,²⁴ DeWolfe²⁵ has described the synthesis of several *N,N'*-diarylacetamidines by heating equimolar mixtures of ethyl *N*-arylacetimidates with aromatic primary amines in the presence of *p*-toluenesulfonic acid, as well as by prolonged heating of a mixture of two moles of aromatic amine and one mole of ethyl orthoacetate in the presence of a trace of *p*-toluenesulfonic acid. Apparently acetic acid is a much more effective catalyst for this reaction, particularly when it is present in molar quantities, for comparison of our results with those of DeWolfe reveals that amidine formation from aromatic primary amines and ethyl orthoacetate takes place rapidly and in good yield in the presence of (usually) molar quantities of acetic acid, but that imido ester formation becomes predominant when the amount of acetic acid is decreased. This latter observation agrees well with DeWolfe's observation that heating equimolar mixtures of ethyl orthoacetate and aromatic primary amines results in formation of the corresponding ethyl *N*-arylacetimidates in high yield.

Experimental²⁶

N,N'-Dicyclohexylformamidine.—A mixture of 74.0 g. (0.50 mole) of ethyl orthoformate and 30.0 g. (0.50 mole) of glacial acetic acid was heated to boiling (under reflux) by an oil bath held at 140–150°. To this mixture was added dropwise, during a period of 30 min., 99.0 g. (1.0 mole) of cyclohexylamine. The reaction mixture was then allowed to reflux for 45 min., the bath temperature was raised to 155° and the volatile material allowed to distil. The flask containing the residual liquid was cooled to room temperature and evacuated overnight at 0.5 mm. By morning a solid mass of crystals (132 g.) had formed. Recrystallization of a 10.0-g. sample of this material from cyclohexane-benzene (6:4) gave 8.60 g. (85%) of white crystals of *N,N'*-dicyclohexylformamidine acetate; m.p. 134–136.5°.

(20) A. J. Hill and I. Rabinowitz, *J. Am. Chem. Soc.*, 48, 732 (1926).

(21) A. J. Hill and M. V. Cox, *ibid.*, 48, 3214 (1926).

(22) E. Lippmann, *Ber.*, 7, 541 (1874).

(23) A. Pinner, "Die Imidoäther und ihre Derivate," Berlin, 1892.

(24) W. A. Ehrhart, doctoral dissertation, Princeton University, 1960; Univ. Microfilms, order no. 61-4705; *Dissertation Abstr.*, 22, 2193 (1962).

(25) R. H. DeWolfe, *J. Org. Chem.*, 27, 490 (1962).

(26) We are indebted for the microanalyses to Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 67.1; H, 10.5; N, 10.4. Found: C, 67.3; H, 10.6; N, 10.3.

A sample of the crude product was shaken with aqueous sodium carbonate and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the white residue from 60–70° petroleum ether gave white crystals, m.p. 102–104°. The reported melting point for *N,N'*-dicyclohexylformamidinium is 106°.¹⁷

A solution of this amidine in ether was treated with picric acid to give a picrate which was recrystallized from benzene; m.p. 225–227.5°.

Anal. Calcd. for $C_{15}H_{15}N_3O_7$: C, 52.2; H, 6.2; N, 16.0. Found: C, 52.4; H, 6.3; N, 16.2.

N,N'-Dibenzylformamidinium.—A mixture of 17.0 g. (0.115 mole) of ethyl orthoformate and 6.9 g. (0.113 mole) of acetic acid was heated under reflux by means of an oil bath maintained at 150°, and 24.6 g. (0.23 mole) of benzylamine was added from a dropping funnel as rapidly as possible without flooding the condenser. The reaction mixture was heated under reflux for 2 hr., the condenser was set for distillation and the mixture was allowed to distil until all volatile material had been removed. The remaining viscous liquid (33.7 g.) was shaken in a separatory funnel with ether, the ether layer discarded, and the aqueous layer made alkaline by the addition of solid sodium carbonate. Extraction with ether, evaporation of the ether extract, and crystallization of the solid residue from 30–60° petroleum ether gave 17.6 g. (68%) of white needles, m.p. 75.5–77.5°. The reported melting point for *N,N'*-dibenzylformamidinium is 76–77°.¹⁷

N,N'-Di-*n*-butylformamidinium.—This material was prepared from *n*-butylamine, ethyl orthoformate and acetic acid as described above. The residual liquid after evaporation of ether was purified by distillation at 85–87°/0.09 mm. and the free amidine was obtained in 55% yield. The recorded boiling point for this material is 103–104°/4.0 mm.¹⁷ Addition of the product to alcoholic picric acid gave a picrate which, upon recrystallization from ethanol, melted at 117.5–119°. The recorded melting point for the picrate of *N,N'*-di-*n*-butylformamidinium is 114.5–116.5°.²²

N,N'-Di-*n*-propylformamidinium.—A mixture of 74.0 g. (0.50 mole) of ethyl orthoformate and 30.0 g. (0.50 mole) of acetic acid was heated to boiling under reflux by means of an oil bath maintained at 130–140°, and 59.0 g. (1.0 mole) of *n*-propylamine added dropwise over a period of 10 min. The resulting mixture was heated for 1.5 hr., the oil bath temperature raised to 155° and volatile material removed by distillation to give 101 g. of a yellow residual oil. A 15.2-g. sample was distilled at 0.70 mm. and the fraction boiling at 97–100° collected; yield, 8.80 g. (62%). A second distillation at 93–94°/0.45 mm. afforded an analytical sample of *N,N'*-di-*n*-propylformamidinium acetate.¹⁹

Anal. Calcd. for $C_{15}H_{25}N_3O_2$: C, 57.4; H, 10.7; N, 14.9. Found: C, 57.4; H, 10.9; N, 14.25.

A 35.0-g. sample of the crude acetate salt obtained as described above was treated with aqueous sodium carbonate and the solution extracted with ether. Evaporation of the dried ether extract and distillation of the residue at 53–55.5°/0.65 mm. yielded 4.0 g. (18%) of a colorless liquid.

Anal. Calcd. for $C_7H_{13}N_3$: C, 65.6; H, 12.6; N, 21.85. Found: C, 65.6; H, 12.5; N, 21.7.

The picrate, prepared in the usual manner and recrystallized from ethanol, melted at 116.5–117°.

Anal. Calcd. for $C_{15}H_{15}N_3O_7$: C, 43.7; H, 5.4; N, 19.6. Found: C, 44.0; H, 5.3; N, 19.8.

N,N'-Dimethylformamidinium.—A mixture of 148 g. (1.0 mole) of ethyl orthoformate and 60 g. (1.0 mole) of acetic acid was heated under reflux by means of an oil bath maintained at 130–140°, while a rapid stream of methylamine was passed through. After 1.25 hr., volatile constituents were removed by distillation from a bath held at 155°. The residual liquid (125.5 g.) was distilled at 82–90°/0.6 mm. to give 112 g. of a colorless liquid which was shown by analysis and by conversion to the picrate, m.p. 166–167.5°, to be at least 80% *N,N'*-dimethylformamidinium.

Anal. Calcd. for $C_6H_{11}N_3O_2$: C, 35.9; H, 3.7; N, 23.25. Found: C, 36.1; H, 3.8; N, 23.3.

An analytical sample of *N,N'*-dimethylformamidinium acetate could not be obtained, even after repeated redistillation. The

chloroplatinate, prepared from the distillate, melted with decomposition at 180–182° (reported m.p. 172°¹⁶).

N,N'-Dicyclohexylacetamidinium.—To a flask containing 39.6 g. (0.40 mole) of cyclohexylamine was added, in portions and with swirling and cooling, 12.0 g. (0.20 mole) of glacial acetic acid. The resulting solid mass was heated in an oil bath held at 150°, and 32.4 g. (0.20 mole) of ethyl orthoacetate added dropwise over 25 min.²¹ Volatile material was allowed to distil as it formed, and distillation continued until the temperature of the vapor in the side arm of the distilling head fell below 75°. The residue (68.3 g.) solidified upon cooling. Recrystallization of a 5.0-g. sample of this crude solid from 60–70° petroleum ether containing 25% benzene gave 3.75 g. (91%) of white crystals, m.p. 93–95°, of *N,N'*-dicyclohexylacetamidinium acetate.

Anal. Calcd. for $C_{18}H_{29}N_3O_2$: C, 68.0; H, 10.7; N, 9.9. Found: C, 68.0; H, 10.8; N, 9.9.

The picrate, prepared in the usual manner in ether solution, was recrystallized from benzene; m.p. 169.5–171.5°.

Anal. Calcd. for $C_{19}H_{29}N_3O_7$: C, 53.2; H, 6.5; N, 15.5. Found: C, 53.3; H, 6.7; N, 15.25.

N,N'-Dibenzylacetamidinium.—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate, 21.4 g. (0.20 mole) of benzylamine, and 6.0 g. (0.10 mole) of glacial acetic acid was heated under reflux for 1 hr. at a bath temperature of 130–140°, and then volatiles were removed at a bath temperature of 155°. The residual liquid (31.25 g.) was treated with aqueous sodium carbonate. Ether extraction and distillation at 202–211°/0.75 mm. gave 17.3 g. (73%) of a colorless liquid.

Anal. Calcd. for $C_{18}H_{19}N_3$: C, 80.6; H, 7.6; N, 11.8. Found: C, 80.5; H, 7.5; N, 11.8.

The hydrochloride salt, prepared by passing hydrogen chloride into an ether solution of the free amidine, was recrystallized from ethyl acetate–ethanol to give colorless crystals; m.p. 182–184.5°.

Anal. Calcd. for $C_{18}H_{19}N_3Cl$: C, 69.9; H, 7.0; N, 10.2; Cl, 12.9. Found: C, 69.8; H, 6.75; N, 10.4; Cl, 12.7.

N,N'-Dibenzylacetamidinium could be prepared in 41% yield by heating a mixture of 16.2 g. of ethyl orthoacetate and 21.4 g. of benzylamine for 7 hr. at a bath temperature of 130–140°, followed by isolation as described above.

2-Methyl-Δ²-imidazoline.—The acetate salt was prepared in 85% yield by heating equimolar amounts of ethyl orthoacetate, ethylenediamine, and acetic acid for 30 min. at a bath temperature of 130–140°, followed by removal of volatile materials by distillation at 155° and recrystallization of the residue from a mixture of benzene and 30–60° petroleum ether. A final recrystallization from acetone–chloroform gave white crystals; m.p. 94.5–95.5°.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 50.0; H, 8.4; N, 19.5. Found: C, 50.2; H, 8.4; N, 19.3.

The free base was best prepared (in 67% yield) by heating equimolar amounts of ethyl orthoacetate and ethylenediamine under reflux at a bath temperature of 150° for 94 hr., followed by removal of volatile material by distillation and recrystallization of the solid residue from benzene–cyclohexane followed by recrystallization from ethyl acetate. The product melted at 104–105° (lit. m.p. 105, 103, 99–100°²³).

N,N'-Diphenylacetamidinium.—A mixture of 8.1 g. (0.05 mole) of ethyl orthoacetate, 9.3 g. (0.10 mole) of aniline, and 0.25 ml. (0.004 mole) of glacial acetic acid was heated under reflux for 2 hr. by means of an oil bath maintained at 130–140°. Ethanol and unchanged starting material were removed by distillation at 47 mm. from an oil bath held at 225°. The residual liquid solidified upon cooling. Recrystallization from 60–70° petroleum ether–benzene gave 8.0 g. (76%) of white crystals, m.p. 134–135°.

(30) This amidine was previously prepared similarly by Rockwell,¹⁴ but without the deliberate use of acid. Our experiments on this reaction are summarized in Table II and clearly indicate the beneficial effect of acid.

(31) In the orthoformate series the reverse procedure of dropping amine into a hot mixture of ortho ester and acid was used. This proved unsatisfactory for ethyl orthoacetate as this compound is decomposed fairly rapidly by acetic acid under these conditions. Rapid mixing of all ingredients at room temperature is also satisfactory provided the exothermic reaction can be controlled.

(32) A. Ladenburg, *Ber.*, **27**, 2952 (1894).

(33) A. J. Hill and R. S. Aspinall, *J. Am. Chem. Soc.*, **61**, 822 (1939).

(34) H. Bama and L. Donnaschke, *Ber.*, **95**, 1640 (1962). After the present investigation was completed, these workers described an essentially identical preparation of 2-methyl-Δ²-imidazoline (in 75% yield) by heating ethyl orthoacetate and ethylenediamine in the presence of ethylenediamine dihydrochloride or *p*-toluenesulfonyl chloride, while removing ethanol continuously by distillation.

(27) J. S. H. Davids, W. G. M. Jones, and Imperial Chemical Industries, British Patent 583,190 (December 11, 1946).

(28) T. L. Davis and W. E. Yelland, *J. Am. Chem. Soc.*, **59**, 1998 (1937).

(29) The fact that such salts can be distillable liquids has both precedent [J. L. Riebsomer, *ibid.*, **70**, 1629 (1948)] and rationale [J. Walker, *J. Chem. Soc.*, 1896 (1949)].

This material is reported to melt at 133–134.5°, 131–132°, and at 134.5–136°.²⁵

Ethyl *N*-Phenylacetimidate.—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate and 9.3 g. (0.10 mole) of aniline was heated under reflux for 1.5 hr. by means of an oil bath maintained at 130–140°. The bath temperature was then raised to 160° and volatile material distilled. Distillation of the residue at 1.75 mm. gave a single fraction, b.p. 71.5–73.5°; yield, 14.3 g. (88%). The boiling point at atmospheric pressure was 213–215°; ethyl *N*-phenylacetimidate is reported to boil at 207–208°.¹⁸

Anal. Calcd. for C₁₀H₁₃NO: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.7; H, 8.2; N, 8.7.

The residue from the vacuum distillation above was recrystallized from petroleum ether (60–70°) to give 0.55 g. (5.2%) of a white solid, m.p. 133.5–135.5°, which was identical with an authentic sample of *N,N'*-diphenylacetamidine.

***N,N'*-Bis(*o*-methoxyphenyl)acetamidine.**—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate, 24.6 g. (0.20 mole) of *o*-anisidine, and 6.0 g. (0.10 mole) of glacial acetic acid was heated under reflux by means of an oil bath maintained at 130–140°. After 1.3 hr., the temperature was raised to 155° and volatile material was removed under vacuum. A 10.0-g. sample of the residual sirup (34.7 g.) was shaken in a separatory funnel with a mixture of 100 ml. of ether, 100 ml. of water and 3.8 g. of sodium carbonate. The ether layer was separated, the aqueous layer washed several times with ether, and the combined ether extracts dried over sodium sulfate and evaporated to a small volume under reduced pressure. Recrystallization of the solid residue from petroleum ether (b.p. 60–70°) gave 5.6 g. (72%) of white crystals; m.p. 96–97°. This compound is reported to melt at 99°.²⁵

Anal. Calcd. for C₁₈H₁₈N₂O₂: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.1; H, 6.8; N, 10.4.

***N,N'*-Di-*o*-tolylacetamidine.**—A mixture of 8.1 g. (0.05 mole) of ethyl orthoacetate, 10.7 g. (0.10 mole) of *o*-toluidine, and 3.0

g. (0.05 mole) of glacial acetic acid was treated as described in the experiment above. Recrystallization of the crude product, obtained in 57% yield, from petroleum ether (b.p. 60–70°) gave colorless crystals; m.p. 69–70.5°. This material is reported to melt at 69, 65, 136, and 140.5°.²⁵

Anal. Calcd. for C₁₈H₁₈N₂: C, 80.6; H, 7.6; N, 11.8. Found: C, 80.9; H, 7.8; N, 11.8.

***N,N'*-Bis(*o*-chlorophenyl)acetamidine.**—A mixture of 8.1 g. (0.05 mole) of ethyl orthoacetate, 12.75 g. (0.10 mole) of *o*-chloroaniline, and 2.0 g. (0.03 mole) of glacial acetic acid was heated under reflux by means of an oil bath maintained at 130–140° for 2 hr., the bath temperature was raised to 160°, and the volatile material was distilled under vacuum (0.75 mm). Recrystallization of the residue from petroleum ether (b.p. 60–70°) gave 4.0 g. (30%) of glittering, fluffy white needles; m.p. 94.5–95.5°.

Anal. Calcd. for C₁₄H₁₀N₂Cl₂: C, 60.2; H, 4.3; N, 10.0; Cl, 25.4. Found: C, 60.1; H, 4.5; N, 10.0; Cl, 25.3.

***N,N'*-Bis(*p*-nitrophenyl)acetamidine.**—A mixture of 16.2 g. (0.10 mole) of ethyl orthoacetate, 7.9 g. (0.10 mole) of pyridine, 27.6 g. (0.20 mole) of *p*-nitroaniline, and 6.0 g. (0.10 mole) of glacial acetic acid was treated as described in the experiment above. Unchanged *p*-nitroaniline was removed from the crude product by trituration with a small amount of hot ethanol. The residue was then recrystallized from a large volume of ethanol to give the desired product, m.p. 262–264°, in 25% yield. This compound is reported to melt at 261–262°.⁴¹

Anal. Calcd. for C₁₄H₁₂N₄O₄: C, 56.0; H, 4.0. Found: C, 55.6; H, 4.2.

(36) O. Wallach, *Ann.*, **214**, 193 (1882).

(37) Weller-ter Meer in Friedländer's "Fortschritte der Theerfarbenfabrikation," Vol. 14, 1921, p. 409.

(38) O. Wallach and M. Wüsten, *Ber.*, **16**, 144 (1883).

(39) A. Ladenburg, *ibid.*, **10**, 1260 (1877).

(40) Pyridine aids in the dissolution of the otherwise poorly soluble *p*-nitroaniline.

(41) W. Bradley and I. Wright, *J. Chem. Soc.*, 640 (1956).

t-Carbinamines Derived from Partially Hydrogenated Fluorenes and Dibenzofuranes

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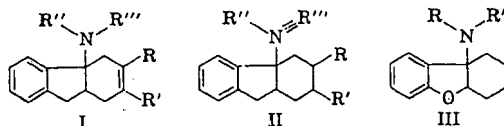
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Received March 15, 1968

Synthetic pathways leading to the preparation of 1,4,4a,9a-tetrahydro-4a-fluorenamines (type I) and 1,2,3,4,4a,9a-hexahydro-4a-fluorenamines (type II) have been investigated. One method which has been elaborated features the Diels-Alder reaction of indene-3-carboxylic acid or its ester with various dienes to yield VIII or IX. The corresponding carboxamides (X), upon Hofmann degradation, have afforded tetrahydrofluorenamines of type I, which upon reduction provide hexahydrofluorenamines II. The latter have also been obtained by intramolecular cyclizations of lithio-imines (XXVII). The 1,2,3,4,4a,9a-hexahydro-4a-N-methylfluorenamine obtained by cyclizing XXVII (R = CH₃) has been found to be identical with the one obtained via the Diels-Alder sequence, indicating that ring-closures of lithio-imines proceed with the formation of *cis*-fused ring systems. Extension of this method has led to the preparation of a number of 5a,6,7,8,9a-hexahydro-9a-dibenzofuranamines (type III). Compounds of types I, II, and III have exhibited potent central nervous system depressant activities.

During the course of investigations leading to the synthesis of biologically active amines it was of interest to prepare a number of partially hydrogenated polycyclic systems bearing angular amino functions.

In this paper we wish to report the preparation of 1,4,4a,9a-tetrahydro-4a-fluorenamines (I), 1,2,3,4,4a,9a-hexahydro-4a-fluorenamines (II), and 5a,6,7,8,9a-hexahydro-9a-dibenzofuranamines (III).



Examination of the literature indicated that of all the possible tetrahydro- and hexahydrofluorenamines only the 9-amino isomers (IV) have been reported.^{1b}



(1) (a) Research Laboratories, Dr. Janssen Beerse, Belgium; (b) S. Fujise, *Rept. Japan. Assoc. Advan. Sci.*, **17**, 44 (1942) [*Chem. Abstr.*, **44**, 3927b (1950)]; Y. Nakamura, *J. Chem. Soc. Japan*, **61**, 1051 (1949); S. Huzisa, *Ber.*, **71**, 2461 (1938).