dibenzylacetonitrile, m. p. 91–92°, and benzyl dibenzyl-cyanoacetate, m. p. 91–92°, respectively. A center cut from (c) was pure benzyl benzylcyanoacetate (XXI), b. p. 180–183° (1 mm.), $n^{25}D$ 1.5533, d^{25}_4 1.124.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3. Found: C, 77.5; H, 5.7; N, 5.3.

From a similar run of 0.13 mole of methyl benzylcyano-acetate, in which the alkaline catalyst was not removed, a partial decarboxylation occurred during the distillation as indicated by an increase in the pressure and a gain in weight of an Ascarite tube in the system. The products of this run were: (a) 3.9 g. (23%) of hydrocinnamonitrile, b. p. 78–92° (1 mm.); (b) 8.0 g. of dibenzylacetonitrile, b. p. 158–170° (1 mm.); and (c) 8.0 g. of an oil, b. p. 180–220° (1 mm.), which crystallized on cooling. Recrystallization of (b) from ethanol gave pure dibenzylacetonitrile, m. p. 91–92°. Extraction of (c) with ether left 2.9 g. (7%) of tribenzylacetonitrile (XIX), m. p. 210–217°, which after recrystallization from a chloroform–alcohol mixture gave white needles, m. p. 222–223.5°.

Anal. Calcd. for $C_{23}H_{21}N$: C, 88.7; H, 6.8; N, 4.5. Found: C, 88.1; H, 7.0; N, 4.5.

Tribenzylacetonitrile is insoluble in cold, concentrated sulfuric acid, but dissolves when the acid is warmed to 95–100° to give a pale yellow solution, which yields no precipitate on dilution with water. The nitrile (XIX) is recovered unchanged after heating with 75% (by volume) sulfuric acid at 100–125° for five minutes or with refluxing 50% sulfuric acid for fourteen hours; under the former set of conditions dibenzylacetonitrile (XVIII) is converted in good yield to dibenzylacetamide, which, after recrystallization from ethanol–water, melts at 127–129°.

The ether extract from which XIX was separated was distilled and gave an additional 3.2 g. of dibenzylaceto-nitrile (total yield, 39%) and 2.5 g. (5%) of benzyl dibenzylcyanoacetate, b. p. 200–220° (0.7 mm.), which crystallized on standing and which after recrystallization from ethanol melted at 91–92°.

Summary

Cyanoketene dimethyl- and diethylacetals have been prepared by the pyrolysis of the corresponding orthoesters and certain of their properties and reactions reported.

With one equivalent of benzyl bromide the dimethylacetal gives methyl dibenzylcyanoacetate as one of the reaction products, showing that the negative cyano substituent makes possible the replacement of the single methylene hydrogen of the acetal.

In the presence of a second equivalent of benzyl bromide the reaction continues with the methyl esters produced by the first equivalent to yield benzyl esters of mono- and dibenzylcyanoacetates, which lose carbon dioxide to yield mono-, di- and tribenzylacetonitriles.

These novel benzylation reactions are also shown to occur with these methyl esters and benzyl alcohol.

MADISON, WISCONSIN   RECEIVED AUGUST 14, 1948

Ketimines and Acylketimines Related to Amidone[1]

BY L. C. CHENEY, R. R. SMITH AND S. B. BINKLEY

Because of the great importance of morphine and related opium alkaloids in medicine and the associated problem of liability to drug addiction, it is not surprising that information pertaining to the discovery of the potent analgesic drug, amidone (I)[2a,b] has already stimulated rather extensive chemical and clinical investigation.[3–18]

(1) Presented before the Medicinal Division of the American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(2) (a) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of Publication Board, Department of Commerce, Washington, D. C., p. 96; (b) B. I. O. S. Final Report, No. 116, Item No. 24, pp. 51, 56, 65.

(3) Scott and Chen, *J. Pharmacol.*, **87**, 63 (1946).

(4) Scott, Robins and Chen, *Science*, **104**, 587 (1946).

(5) Thorp, *Brit. J. Pharmacol.*, **1**, 113 (1946).

(6) Thorp, Walton and Ofner, *Nature*, **159**, 679 (1947).

(7) Easton, Gardner and Stevens, THIS JOURNAL, **69**, 976, 2941 (1947).

(8) Gentling and Lundy, *Proc. Mayo Clinic*, **22**, 249 (1947).

(9) Elliott, *Fed. Proc.*, **6**, 327 (1947).

(10) Thorp, Walton and Ofner, *Nature*, **160**, 605 (1947).

(11) Blicke and Zambito, paper presented before the Division of Medicinal Chemistry, the American Chemical Society, Atlantic City, N. J., April 16, 1947.

(12) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

(13) Brode and Hill, *ibid.*, **69**, 724 (1947).

(14) Scott, Kohlstaedt and Chen, *Anesthesia & Analgesia*, **26**, 12 (1947).

(15) Hewer and Keele, *Lancet*, **2**, 28 (1947).

(16) Eddy, *J. Am. Pharm. Assoc.*, **8**, 537 (1947).

Inasmuch as it has been reported[19] that nuclear substitution of the two phenyl groups in amidone does not enhance analgesic potency or lead to more desirable activity, attention has been focused in this Laboratory on other structural modifications, including the synthesis of certain carbinols, esters,[20] ketimines and acylated ketimines related to amidone. Several examples of the latter class have been described by other investigators[7,12,17] since the completion of this work.

Although ketimines are commonly dealt with as unstable intermediates in the synthesis of ketones by means of the Grignard reagent[21] and the Hoesch and Hoesch–Houben syntheses, few, if any, imines or acylimines of physiologically active ketones appear to have been studied pharmacologically. Our interest was initially aroused in this class of compounds when the remarkably stable isoamidone imine (II)[12,17] was unexpectedly isolated while carrying out the synthesis of amidone in essential accordance

(17) Easton, Gardner, Evanick and Stevens, THIS JOURNAL, **70**, 76 (1948).

(18) Schultz and Sprague, *ibid.*, **70**, 48 (1948).

(19) Reference 1, p. 93.

(20) Speeter, Byrd and Cheney, *ibid.*, **71**, 57 (1949).

(21) Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft m. b. H., Stuttgart, 1944, pp. 500, 587.

TABLE I

$(C_6H_5)_2RC$—$C(=NR^1)C_2H_5$ KETIMINES AND ACYL DERIVATIVES

No.	R	R¹	Formula	M. p. or b. p. °C.
412-10H	—CH₂—CH₂—NC₄H₈O	H	$C_{22}H_{28}N_2O$	198–202 (1 mm.)
412-12H	—CH₂—CH₂—NC₅H₁₀	H	$C_{23}H_{30}N$	191–193 (1 mm.)
C-11912-B	—CH—CH₂—N(CH₃)₂ (CH₃)	H	$C_{21}H_{28}N_2 \cdot HCl$ $C_{21}H_{28}N_2 \cdot 2HCl^c$	151–152 205–206 (dec.)
317-12	—CH₂—CH—N(CH₃)₂ (CH₃)	H	$C_{21}H_{28}N^d$	54–56
489-7H	—CH₂—CH—N(CH₃)₂ (CH₃)	O=C—CH₃	$C_{23}H_{30}N_2O^e$ $C_{23}H_{30}N_2O \cdot HCl^e$	134–135 219–220
C-14719B	—CH—CH₂—N(CH₃)₂ (CH₃)	O=C—CH₃	$C_{23}H_{30}N_2O \cdot HCl^e$	214–215
489-16H	—CH₂—CH₂—NC₄H₈O	O=C—C₂H₅	$C_{26}H_{32}N_2O_2 \cdot HCl$	231–232.5
489-43H	—CH₂—CH—N(CH₃)₂ (CH₃)	O=C—C₂H₅	$C_{24}H_{32}N_2O$ $C_{24}H_{32}N_2O \cdot HCl$	146–147 202–203
412-16H	—CH₂—CH₂—NC₅H₁₀	O=C—CH₃	$C_{25}H_{32}N_2O \cdot HCl$	209–210
412-11H	—CH₂—CH₂—NC₄H₈O	O=C—CH₃	$C_{24}H_{30}N_2O_2 \cdot HCl$	202–203

with the original procedure.[1] For the sake of convenience lithium amide was advantageously substituted for sodium amide in the condensation of diphenylacetonitrile with 1-dimethylamino-2 chloropropane. The oily reaction product proved
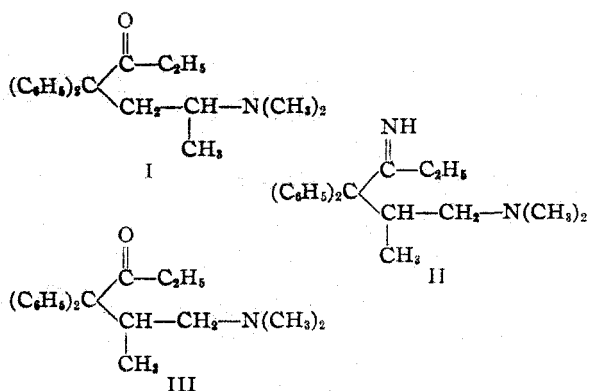
to be a mixture of isomeric nitriles[12,18] which yielded amidone (I) and isoamidone imine (II) on treatment with ethylmagnesium bromide followed by hydrolysis in accordance with the original directions.[1] In order to ensure complete hydrolysis, the ketimine (II) was refluxed with constant boiling hydrochloric acid for thirty-six hours, whereupon isoamidone (III)[7,8,10,17] was obtained in quantitative yield. The preparation of the dihydrochloride and the acetyl derivative completed the characterization of isoamidone imine.

It is noteworthy that ketimines of the iso-amidone series are not appreciably hydrolyzed

under the drastic conditions imposed by the German procedure for the preparation of amidone, for sufficient heat is evolved to volatilize practically all of the xylene used as the solvent when the Grignard reaction product is poured into the dilute hydrochloric acid. Other examples of sterically hindered, stable ketimines, however, can be found in the literature. Typical examples are the ketimines of trichloroacetomesitylene[22] and 1,2-diphenyl-2-methyl-1-propanone.[23]

The less sterically hindered and consequently less stable ketimines were isolated in favorable yields by conducting the hydrolysis of the bromo-magnesium salt in the cold with ammonium chloride. The imines were then extracted with ether from basic solution and purified by distillation in vacuo. They are all low-melting solids or viscous yellow oils, some of which gradually evolve ammonia on standing at room temperature. Precipitation of the ketimines from ethereal solution with hydrogen chloride produced hygroscopic acidic salts which melted over a wide range with the evolution of gas. Cloke[24] has noted a similar phenomenon in working with other ketimines. The acylketimines were prepared by treating a benzene solution of the imine with the appropriate acid chloride or, alternatively, by adopting the general procedure of Moureau and Mignonac[25] and adding dropwise the acid chloride directly to the cold bromo-magnesium salt of the ketimine.

(22) Houben and Fischer, Ber., **63**, 2455 (1930).
(23) Bruzau, Compt. rend., **190**, 496 (1930).
(24) Cloke, THIS JOURNAL, **62**, 117 (1940).
(25) Moureu and Mignonac, Compt. rend., **170**, 1353 (1920).

Table I (Continued)

Recryst. from	Calculated C	Calculated H	N	Found C	Found H	N	Mouse I. P. LD/50[a]	S. C.[a] g. pig anal. dose	Activity[b] index
	78.6	8.39	8.33	78.5	7.85	8.38	136 ± 15.7	15	9.1
	82.7	9.04	8.38	82.4	8.96	8.30	56 ± 11.4	12.5	4.5
Isopropyl alcohol	73.2	8.48	8.13	73.2	8.65	8.26	60.5 ± 9	15	4
Acetone	66.3	7.88		66.2	7.71				
Skellysolve A			9.04			8.7	41 ± 3	12.5	3
Skellysolve B	78.8	8.62		78.7	8.63				
Ethyl acetate	71.4	8.08		71.5	7.96		151 ± 1.2	12.5	12
Abs. alcohol–ether	71.4	8.08	7.28	70.7	8.08	6.97	171 ± 7	30	5.7
Abs. alcohol–ether	70.0	7.76		70.5	7.38		67 ± 8	12.5	5.4
Abs. alcohol	79.2	8.86	7.69	79.3	9.40	7.22			
Ethyl acetate	72.0	8.3	7.0	71.4	8.04	6.68	122 ± 7	25	4.9
Dioxane	72.6	8.08	6.78	72.3	7.91	7.14	187 ± 11.7	50	3.7
Acetone	69.7	7.55		69.2	7.35		232.8 ± 33.2	75	3.1

[a] Values expressed with standard error in milligrams per kilogram. [b] Comparative values for amidone: LD/50 = 29 ± 1.7, analgesic dose = 12.5, activity index = 2.3; for isoamidone: LD/50 = 39 ± 2.8, analgesic dose = 12.5, activity index = 3.1. [c] References 7, 12 and 17. [d] Prepared by Dr. M. E. Speeter. [e] Reference 17.

Experimental

Preparation and Separation of 4-Dimethylamino-2,2-diphenyl-3-methylbutyronitrile and 4-Dimethylamino-2,2-diphenylvaleronitrile.—The following procedure is believed to offer some advantages over the published method.[12] To a well-stirred suspension of 36.3 g. (1.58 moles) of lithium amide in 285 ml. of dry benzene there was added 278 g. (1.44 moles) of diphenylacetonitrile over a period of twenty minutes while the temperature was maintained at 45–50°. After the addition was completed, the mixture was heated at 45–50° for one and one-half hours. It was then cooled to 20–25° and 181.1 g. (1.49 moles) of 1-dimethylamino-2-chloropropane[1] was added. The mixture was stirred for one hour and then heated gradually until a vigorous reaction ensued with the evolution of ammonia. Heating was discontinued until the reaction moderated, whereupon the mixture was refluxed for an additional two hours, then cooled and poured into 800 ml. of water. The benzene layer was separated, washed twice with water and extracted with 6 N hydrochloric acid until a precipitate no longer formed in a sample of extract when made basic. The combined extracts were washed once with ether, made strongly alkaline with sodium hydroxide solution and extracted with a total of 700 ml. of ether in three portions. After the combined ether extracts were washed with water and saturated salt solution, they were dried over anhydrous potassium carbonate and the filtered solution was concentrated and cooled to induce crystallization of the higher melting nitrile, which was collected by filtration. Further concentration and cooling led to the total isolation of 187.5 g. (46.8% yield) of 4-dimethylamino-2,2-diphenylvaleronitrile,[12,13] m. p. 90–91°.

The removal of residual ether left a viscous yellow-brown oil which was dissolved in 200 ml. of absolute alcohol, and treated with an excess of absolute alcoholic hydrogen chloride. Small white crystals of the aminonitrile hydrochloride (145.5 g.), m. p. 222–225°, separated. Recrystallization from absolute alcohol (350 ml.) elevated

the melting point to 225–226°. The purified hydrochloride (119.4 g.) was dissolved in water, made alkaline with ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried over potassium carbonate, and solvent was removed to obtain 103.2 g. (25.8% yield) of 4-dimethylamino-2,2-diphenyl-3-methylbutyronitrile,[12,13] in the form of a colorless oil which crystallized on scratching and cooling to melt at 67.5–69°. The structure of each isomer has been definitely established.[12]

Repeated attempts to detect the presence of a third aminonitrile, the precursor of Isoamidone I,[7,17] as a product of the alkylation were unsuccessful.

The other alkylations of diphenylacetonitrile were conducted in accordance with the above procedure. When isomeric aminonitriles were not involved, the product was readily purified by distillation through a Vigreux column.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (Isoamidone) (III) Hydrochloride[7,10,17] Monohydrate.—4-Dimethylamino-2,2-diphenyl-3-methylbutyronitrile was converted into isoamidone imine (II)[12,17] in accordance with the general procedure described for the preparation of ketimines. The product, b. p. 148–153° at 1 mm., was obtained in 76.7% yield. Treatment of an isopropyl alcohol solution of the base with one equivalent of hydrogen chloride followed by dilution with ether precipitated a monohydrochloride monohydrate of II which melted at 89–142°, dec., after being dried in the air. The anhydrous monohydrochloride of II, m. p. 151–152°, was obtained by heating a sample of the hydrate in vacuo, first at 61° for two hours, and then at 81° for three hours.

A mixture of 10 g. (0.0275 mole) of the monohydrochloride monohydrate of II was refluxed for thirty-six hours with 90 ml. of concentrated hydrochloric acid. The solution was cooled in ice and made strongly alkaline by the addition of 50 g. of sodium hydroxide dissolved in 145 ml. of water. Prolonged cooling and scratching with a glass rod failed to crystallize the oily base. It was therefore extracted with 400 ml. of ether and the washed extract was dried for four hours over anhydrous potas-

sium carbonate. To the cooled filtered solution there was added an excess of absolute alcoholic hydrogen chloride. After the white hydrochloride which precipitated was collected and dried *in vacuo* overnight over phosphorus pentoxide, it melted at 119–122° and weighed 9.8 g. The melting point was not altered by recrystallization of a sample from dilute hydrochloric acid by the addition of a saturated solution of sodium chloride. Analyses disclosed that the compound, in spite of its subjection to the drying agents, was actually the monohydrate.

Anal. Calcd. for $C_{21}H_{28}NOCl \cdot H_2O$: C, 69.4; H, 8.33; N, 3.87. Found: C, 68.9; H, 8.23; N, 3.83.

Following recrystallization of the monohydrate from ethyl acetate and desiccation over phosphorus pentoxide, the salt melted at 155–158° with previous softening but still contained water. The anhydrous material has been reported to melt at 190–193°.[17]

4,4-Diphenyl-6-(4-morpholinyl)-3-iminohexane (412-10H).—The general procedure employed for the preparation of the ketimines is illustrated by the following typical example. To the well-stirred solution of ethylmagnesium bromide prepared in the customary manner from 13.4 g. (0.544 mole) of magnesium turnings, 67.9 g. (0.62 mole) of ethyl bromide and 115 ml. of anhydrous ether, there was added during a period of fifteen minutes a solution of 84.9 g. (0.277 mole) of 2,2-diphenyl-4-(4-morpholinyl)-butyronitrile dissolved in 91 ml. of dry xylene. The mixture was stirred and refluxed for four and one-half hours, during which time a greenish gray precipitate formed. A nitrogen atmosphere was provided throughout the reaction. The thick suspension was cooled, diluted with about 100 ml. of ether to facilitate the transfer and poured slowly into a stirred, cooled mixture composed of 150 g. of ice and 300 ml. of water. Following completion of the hydrolysis, 150 ml. of concentrated ammonium hydroxide was added, the ether phase was separated and the aqueous layer extracted twice with 200-ml. portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous potassium carbonate. After the removal of the solvent, distillation through a short Vigreux column afforded 73.8 g. (79.2%) of the ketimine as a pale yellow viscous oil, b. p. 198–202° at less than 1 mm. It separated from ether in the form of colorless crystals, m. p. 85–86.5°.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-(acetylimino)-hexane Hydrochloride[17] (C-14719B).—A cold aqueous solution of 3 g. (0.00875 mole) of II monohydrochloride was made alkaline with 20% sodium hydroxide solution and extracted with 50 ml. of benzene. The benzene layer was washed with water, dried over anhydrous potassium carbonate and filtered. Treatment of the solution with 10.5 ml. of a molar solution of acetyl chloride in benzene (a 20% excess) caused a precipitate to form. After refluxing the mixture for two hours, solvent was distilled under reduced pressure and the white residue was boiled with 25 ml. of ethyl acetate, cooled and filtered to obtain 3 g. (89% yield) of fine white crystals, m. p. 214–215°. A sample was dissolved in hot absolute alcohol and precipitated with ether without changing the melting point.

6-Dimethylamino-4,4-diphenyl-3-(propionylimino)-heptane Hydrochloride (489–43H).—An ethereal solution of ethylmagnesium bromide prepared from 4.9 g. (0.2 mole) of magnesium, 115 ml. of dry ether and 24.5 g. (0.225 mole) of ethyl bromide in a nitrogen atmosphere was treated with 30 g. (0.108 mole) of 4-dimethylamino-2,2-diphenylvaleronitrile dissolved in 200 ml. of dry xylene and the stirred mixture was refluxed for four and one-half hours. The resulting suspension was chilled in an ice–salt-bath throughout the dropwise addition of

20.8 g. (0.224 mole) of propionyl chloride dissolved in 50 ml. of ether. After standing overnight the yellow-green suspension was stirred into a mixture of 300 g. of ice, 150 g. of ammonium chloride and 150 ml. of water. When all solid had dissolved, the solution was made alkaline with ammonium hydroxide, which caused the precipitation of 5.9 g. of the free acylimine, m. p. 142–145°. Upon treatment of the washed and dried ether layer with hydrogen chloride, 31 g. of hydrochloride precipitated which was dissolved in water and converted into 11.3 g. of the crude base, m. p. 139–144°, by the addition of ammonia. Recrystallization of the combined fractions from 65 ml. of ethanol produced 14.2 g. (35% yield) of the pure base, m. p. 146–147°.

The hydrochloride was prepared by dissolving 13.2 g. of the base in 20 ml. of warm benzene, diluting with 200 ml. of dry ether and bubbling an excess of hydrogen chloride into the solution. The strongly acidic salt (15 g.) which precipitated was boiled under reflux with 140 ml. of anhydrous ethyl acetate until no more hydrogen chloride was evolved. Cooling, filtration and desiccation over phosphorus pentoxide afforded 9.3 g. of small white crystals, m. p. 202–203°.

Pharmacology

The pharmacological evaluation of these compounds was conducted by Dr. Carl C. Pfeiffer of the University of Illinois Medical School and the preliminary data are presented here with his permission. White mice injected intraperitoneally were used for the toxicity determinations. A modified Wolff–Hardy technique applied to guinea pigs was used to measure minimal subcutaneous analgesic dosage. Activity index is the mouse LD_{50} divided by the guinea pig analgesic dose, a device which serves as an effective basis for comparison.

From the tabulation it can be observed that in both the amidone and isoamidone series the order of decreasing toxicity and increasing activity index is ketone: ketimine: acetylketimine. Owing to comparable potency and significantly lower toxicity, all of the tabulated ketimines and their acyl derivatives possess as high or more favorable activity indices than those of amidone and isoamidone. With reference to the acylated ketimines, the amidone side chain confers highest potency and index when the acyl group is acetyl. Conversely, in the case of the β-morpholinylethyl compounds the propionyl group is more effective than the acetyl.

It should be mentioned that since the *levo*-isomer of amidone has been shown to be the pharmacologically active form,[2,10] one should expect the *l*-isomer of amidone imine and its acyl derivative to be approximately twice as potent as the tabulated values. Since the intermediate nitrile can be resolved without difficulty,[10] the synthesis of these optically active forms appears practicable.

Summary

Some representative ketimines and acylated ketimines related to amidone have been described. Preliminary pharmacological data indicate that these compounds are potent analgesic drugs which are less toxic than the corresponding ketones.