temperature between 558–562 ± 1°. A titration of the acid and a measure of the carbon dioxide formed (which at no time was greater than 2.8%) served to determine the extent of pyrolysis. The esters were prepared according to the method of Brändström,[3] and the data on their preparation, identification, and pyrolysis are given in Table I.

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Methadon Analogs[1]

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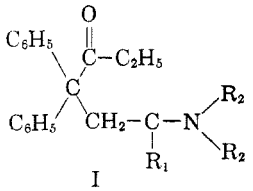
Variations in the structure of methadon [I, R_1 = CH_3, NR_2 = $N(CH_3)_2$] have been made[2,3] without



I

substantial increase in activity, and often with loss of activity. Thus substitution in I (R_1 = C_2H_5) resulted in disappearance of activity,[4] while substitution of $-NR_2$ as morpholine or piperidine afforded retention of analgesic acitvity.[3] Recent studies have critically examined the structural features of methadon analogs which influence activity.[5]

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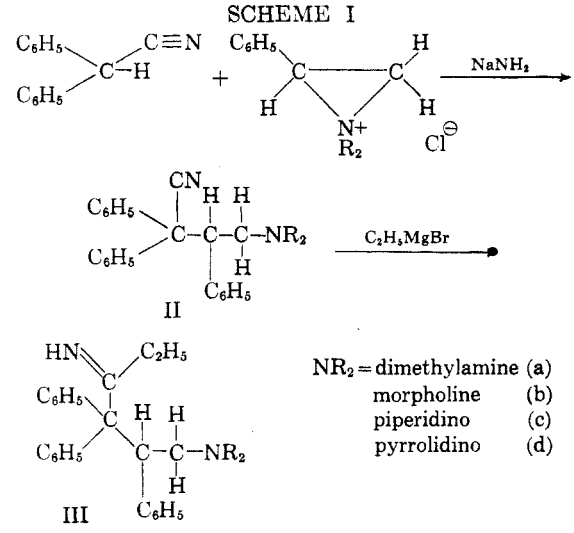
This paper reports the isolation of 1-substituted amino-2,3,3-triphenylhexanimines in the attempted synthesis of I (R_1 = C_6H_5) from the previously described 2-dialkylamino-1-phenethyl chlorides.[6]

The sequence of reactions used is reported as shown in Scheme I.

In earlier work with methadon analogs, the condensation of dialkylaminoisoalkyl chlorides with diphenylacetonitrile has been shown to proceed *via* an ethyleneimonium ion[7] with subsequent reaction at the imonium ion being governed[8] by steric factors, as well as polar factors, both

SCHEME I



within the cyclic ion and in the diphenylacetonitrile anion with which it reacts.

The imonium ion obtained from the 2-dialkylamino-1-phenethyl chlorides would in all probability be more vulnerable to nucleophilic attack[6] by the diphenylacetonitrile anion at the phenyl-bearing carbon to yield the 2,2,3-triphenyl-4-substituted aminobutyronitrile (II). Only one compound was isolable in these condensations. The likelihood of reaction being effected at this more hindered carbon of the imonium ion, is also consistent[9] with the isolation of the ketimines (III).

Considerable difficulty was initially experienced in the isolation of the butyronitriles (II) in view of their unanticipated failure to be extracted into aqueous solvents as their hydrochlorides. The steric influence of the 3-phenyl group in such nitriles is apparent when one considers the ease of hydrochloride formation in analogous compounds wherein

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TABLE I

2,2,3-TRIPHENYL-4-DIALKYLAMINOBUTYRONITRILES (II)
$(C_6H_5)_2C(CN)CH(C_6H_5)CH_2NR_2$

Compounds	NR_2	M.P., °C.[a,b]	Yield, %	Formula[d]	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIa	Dimethylamino	193–195	33	$C_{24}H_{24}N_2$	84.7	84.7	7.1	6.9	8.2	8.0
IIb	Morpholino	178–180	37	$C_{26}H_{26}N_2O$	81.6	81.8	6.9	6.7	7.3	7.1
IIc	Piperidino	180–184[b1]	47	$C_{27}H_{28}N_2$	85.2	85.3	7.4	7.4	7.4	7.1
IId	Pyrrolidino	187–189[b2]	47	$C_{26}H_{26}N_2$	85.2	84.9	7.2	7.1	7.7	7.9
	ETHYL 1,1,2-TRIPHENYL-3-DIALKYLAMINOPROPYL KETAMINES (III) AND RELATED COMPOUNDS									
IIIb	Morpholino	178–181	46	$C_{28}H_{32}N_2O$					6.8	6.7
IIIb[e]	Morpholino	222–226[b3]	52	$C_{28}H_{35}ClN_2O_2$[d1]					5.6	5.8
IIIb[f]	Morpholino	242–245[b4]	25	$C_{28}H_{32}ClNO_2$[d2]	74.7	75.2	7.2	7.3	3.1	3.0
IIIb[g]	Morpholino	64–66[b5]	47	$C_{28}H_{34}N_2O$	81.2	81.2	8.3	8.1	6.8	6.7
IIIb[h]	Morpholino	188–194[b5]		$C_{23}H_{38}Cl_2N_2O_3$[d3]	66.6	66.9	7.6	7.6	5.6	5.4
IIIb[i]	Morpholino	195–197[b1]		$C_{30}H_{34}N_2O_2$	78.9	78.4	8.0	7.7	6.1	6.0
IIIc	Piperidino	181–183	53	$C_{29}H_{34}N_2$					6.7	6.8
IIId[j]	Pyrrolidino	225–227	65	$C_{28}H_{34}Cl_2N_2$[d4]	71.8	71.3	7.1	6.9	6.0	6.2

[a] Melting points are not corrected. [b] Recrystallizing solvent is ethanol unless otherwise shown; [b1] ethyl acetate–hexane; [b2] ethyl acetate; [b3] *n*-propanol; [b4] washed with isopropyl alcohol; [b5] not recrystallized. [c] Analyses by Weiler and Strauss, Oxford, England. [d] Chlorine. Calcd.-Found;[d1] 7.4–7.4; [d2] 7.9–7.7; [d3] 14.0–14.0; [d4] 15.1–14.9. [e] Hydrochloride monohydrate. [f] Hydrochloride of ethyl 1,1,3-triphenyl-3-morpholinopropyl ketone. This compound was isolated in one run following procedures shown in the experimental for preparation of the ketimines. Repetition of the Grignard synthesis yielding a ketone with the morpholino nitrile IIb or with the other nitriles was not successful. [g] 4-Amino-1-morpholino-1,3,3-triphenylheptane. [h] Dihydrochloride-monohydrate of compound of footnote *g*. [i] *N*-Acetyl derivatives of compound of footnote *g*. [j] Dihydrochloride.

this phenyl group is replaced by methyl.[10] Steric hindrance wherein the basic constituent is modified so that it cannot accept a proton has been reported in other systems.[11,12]

The Grignard reaction using ethylmagnesium bromide[13] with II, resulted only in recovery of the reactant nitrile (IIa), and in formation of the ketimines (IIIb, IIIc, and IIId). In one experiment, a compound giving the analysis of the desired ketone corresponding to IIIb was obtained but this could not be repeated. In contrast to the nitriles (II), the ketimines (III) readily formed hydrochlorides. The failure of the *N*-4-dimethylamino-2,2,3-triphenylbutyronitrile (IIa) to condense is consistent with a conformation of the *N*-methyl groups blocking attack by the Grignard reagent at the nitrile group. In contrast, the more sterically restrained *N*-methylene carbons in IIb, IIc, and IId permit the reaction of conversion to the ketimine to occur.

The isolation of ketimines has been previously noted, particularly in the more hindered isomethadon structure[7,9,14–16] and these could be converted to the desired ketones by acid hydrolysis. The ketimines (III) of this work did not respond to hydrolysis using hydrochloric acid reflux, or under sealed tube hydrolysis using concentrated hydrochloric acid, or mixture of hydrochloric acid and acetic acid. The role of steric factors in resistance to ketimine hydrolysis has been previously explored[17,18] with the compounds of type III being substantially invulnerable to hydrolysis. Construction of molecular models indicates complete shielding of the ketimine carbon. It is also relevant that the presence of substituents on the carbon beta to the ketimine group would markedly repress hydrolysis.[19,20]

The morpholino ketimine (IIIb) was reduced to the corresponding amine with lithium aluminum hydride, which in turn was converted to the acetate.

The compounds prepared have been described in Table I.

Pharmacologic evaluation of the ketimines (III) indicated analgesic activity of the order of $^1/_5$ that of methadon for the morpholino derivatives (IIIb), the other compounds being inactive.

EXPERIMENTAL[21,22]

N-4-Morpholino-2,2,3-triphenylbutyronitrile (IIb). A stirred suspension of 7.8 g. (0.2 mole) of sodamide in 30 ml. of tolu-

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ene was maintained at 35° in a nitrogen atmosphere during the 1-hr. addition of a solution of 39 g. (0.2 mole) of diphenylacetonitrile in 100 ml. of toluene. After the addition was complete the reaction mixture was heated under reflux for 3.5 hr., cooled, and 0.7 g. of sodium iodide added. A solution of 2-(4-morpholino)-1-phenethyl chloride [prepared from an aqueous solution of 53 g. (0.2 mole) of the hydrochloride,[6] rendered alkaline with 40% sodium hydroxide, followed by extraction of the liberated base with three 75-ml. portions of toluene which were combined and dried with magnesium sulfate] in toluene was added over 2 hr., maintaining the temperature below 35°. The reaction mixture was heated under reflux for 1.5 hr., cooled to 20°, and treated with 200 ml. of water. At this point some product precipitated and was separated. The toluene layer was separated and the aqueous phase re-extracted with 100 ml. of toluene. The initial precipitate and all toluene fractions were combined and the toluene evaporated. The residue of IIb, triturated with 100 ml. of ethanol, yielded 39 g. (51%).

1-Piperidino-2,3,3-triphenylhexanimine-4 (IIIc). A solution of ethyl magnesium bromide was prepared from 1.2 g. (0.05 mole) of magnesium and 6.5 g. (0.06 mole) of ethyl bromide in 50 ml. of anhydrous ether and treated while refluxing with a solution of 15.2 g. (0.04 mole) of IIc in 90 ml. of hot tetrahydrofuran (dried over calcium hydride) over 1 hr., followed by 60 ml. of hot xylene. During the addition, the internal temperature was raised to 80–85° by partial distillation and so maintained with stirring for 5 hr. Then 40 ml. of 1:1 hydrochloric acid was added with continued heating over 0.5 hr. Dilution with water and standing afforded the crude, sparingly soluble hydrochloride, 17 g., which was converted to the free base with aqueous sodium hydroxide.

4-Amino-1-morpholino-2,3,3-triphenylhexane (IIIb[9], Table I). A refluxing solution of 0.42 g. of lithium aluminum hydride in 50 ml. of ether under nitrogen atmosphere continuously extracted a charge of 4.2 g. (0.01 mole) of IIIb over a period of 20 hr.[23] The cooled, stirred mixture was treated slowly with 35 ml. of 10% aqueous sodium hydroxide, the ether phase decanted, and the aqueous alkaline phase continuously extracted with 100 ml. of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and treated with dry hydrogen chloride, yielding the hydrochloride 2.3 g. (47%), m.p. 188–194°. The hydrochloride was converted to the free base which melted at 64–66°.

The *acetate*[24] was prepared, m.p. 195–197° (hexane–ethyl acetate).

Attempted hydrolysis of ketimines (III). Three g. of IIIb hydrochloride was refluxed for 36 hr. with 30 ml. of hydrochloric acid. Solution was never effected and the IIIb hydrochloride was recovered unchanged.

One g. of IIId hydrochloride and 10 ml. of hydrochloric acid in a sealed tube was maintained at 100° for 2 hr. Solution was never complete, and 0.7 g. of IIId hydrochloride was recovered.

One g. of IIId hydrochloride in 2 ml. of acetic acid and 10 ml. of hydrochloric acid in a sealed tube was maintained at 100° for 6 hr. Solution of IIId in the acid mixture was readily obtained, but only the reactant IIId hydrochloride (0.7 g.) could be recovered.

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(21) Data shown in Table I are not reproduced in the Experimental section.

(22) Representative examples are shown for the general procedures used.

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(24) W. J. Hickinbottom, *Reactions of Organic Compounds*, Longmans, Green and Co., London, 1948, p. 297.

5-Phthalimido-2-tetralone[1]

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Reported here is the preparation of 5-phthalimido-2-tetralone. Some synthetic paths leading to tricyclic diterpenes and related compounds using this tetralone were initiated. Unfortunately, that work was interrputed and no further efforts in that area are now contemplated by us. However, there is continued interest and activity in such synthetic problems by other workers. We believe this tetralone and its method of preparation may be of use to others; apparently it is the only 2-tetralone carrying an amino (or potential amino) group so far prepared.

2-Methoxy-5-naphthylamine[2] (I) was reduced with sodium and alcohol in liquid ammonia. The resulting dihydro compound (enol ether) could be isolated and purified, but for convenience and obtaining maximum yield of the desired ketone, the amine was not isolated, but converted to a phthalimide derivative and subsequently to the 2-tetralone. The resulting 5-phthalimido-2-tetralone was thus obtained in 63% yield from I. The free amino group apparently is not compatible with the keto group; cleavage of the enol ether without blocking the amino group or reduction of the corresponding amino phenol with sodium and alcohol in liquid ammonia gave what appeared to be a polymeric material. The amino group could be converted to an acetamide, but the yield was not as satisfactory as with the phthalimide protecting group.

EXPERIMENTAL[3]

5-Phthalimido-2-tetralone. Sodium (35 g.) was added slowly over a period of 1.5 hr. to a solution of 6-methoxy-1-naphthylamine[2] (100 g.) in liquid ammonia (900 ml.) and 95% ethanol (130 ml.). Water (1 l.) was then added and the mixture extracted with four portions of benzene (total vol., 1 l.). The benzene extract was washed with water and then added to a solution of phthalic anhydride (100 g.) in hot benzene (1.5 l.) which resulted in an immediate precipitate of the phthalamic acid. This crude acid (164 g., m.p. 147–150° dec.) was not purified, but was converted directly to the phthalimide by refluxing a solution of it in glacial acetic acid (500 ml.) for 2 hr. To the hot acetic acid solution was added 5% hydrochloric acid (100 ml.) and after 2 min. the mixture was poured onto ice (2.5 kg.).[4] The precipitated tetralone was separated by filtration, dried (wt., 137 g.), ground to a fine powder, and stirred for 24 hr. with a solution of sodium bisulfite (665 g.) in water (1.2 l.) and 95% ethanol (300 ml.). The addition product was separated by filtration, dried, washed with chloroform, suspended in

(1) Taken from part of the Ph.D. thesis by Ross C. Terrell, 1954, Columbia University.

(2) (a) A. Butenandt and G. Schramm, *Ber.*, 68, 2083 (1935); (b) L. F. Fieser and B. Riegel, *J. Am. Chem. Soc.*, 59, 2561 (1937).

(3) Melting points for analytical samples are corrected; other melting points are uncorrected.