Molecular Asymmetry of Methadon

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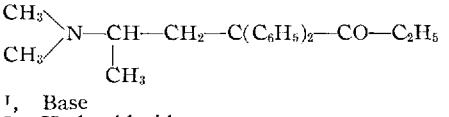
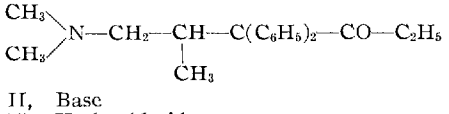
Proton nuclear magnetic resonance spectra of methadon hydrochloride, isomethadon hydrochloride, and related derivatives are recorded and interpreted in terms of a molecular asymmetry and a preferred conformation concept.

SUGGESTIONS relating the potent analgesic activity of methadon (6-dimethylamino-4, 4-diphenylheptan-3-one) (I) and isomethadon (6-dimethylamino-5-methyl-4, 4-diphenylhexan-3-one) (II) with stereochemical considerations of restricted rotation and subsequent molecular asymmetry have been made (1–6) based on indirect evidence of chemical unreactivity of the hindered carbonyl group (7), ultraviolet light absorption and dipole moment measurements (8), dissociation constants (3), and differential analgesic activity of the optical antipodes (9). Proton nuclear magnetic resonance spectra in Table I for several methadon and isomethadon derivatives provide independent evidence for molecular rigidity and for a preferred conformation of the molecule.

These proton spectra have certain features in common, including an acetyl methyl proton triplet, an acetyl methylene quartet, a secondary C-methyl doublet, a 10-proton aromatic signal, and 3 unanalyzed 1-proton multiplets. Whereas the dimethylamino protons of I base appeared as sharp 6-proton singlets at 2.14 p.p.m., the dimethylamino proton signals of salts of I were shifted characteristically downfield (0.6–0.7 p.p.m. except for I*c*) and involved greater multiplicity dependent on salt form, solvent composition, concentration, and temperature.



I, Base
I*a*, Hydrochloride
I*b*, Deuterochloride
I*c*, Sulfur trioxide compound
I*d*, Hydrogen sulfate



II, Base
II*a*, Hydrochloride

Spectra of I*a* were dominated by an unexpected 6-proton 1:2:1 triplet pattern centered about 2.77 p.p.m. The same pattern was observed in 40-Mc. spectra (center at 2.75 p.p.m.). From the slightly different spacings of the 60-Mc. triplet an overlapping doublet of doublets pattern was suspected, and indeed, spectra of solutions cooled in dry ice–acetone exhibited the clearly resolved doublet of doublets pattern. The center of the low-field doublet (J = 5.5 c.p.s.) was separated from the center of the highfield doublet (J = 5.0 c.p.s.) by 10 c.p.s., and as the cooled solution warmed to room temperature the downfield doublet shifted upfield toward the stationary doublet, so that at room temperature a triplet signal was obtained. The triplet was not collapsed by recording the spectra at 60°.

The dimethylamino proton doublet of doublets pattern in I*a* spectra collapsed to a sharp singlet on equilibration of the deuterochloroform solutions with deuterium oxide or by dilution with pyridine. Deuterium oxide solutions of I*a* likewise showed a 6-proton singlet. In contrast, the deuterochloride I*b* exhibited a doublet pattern in suitably dilute deuterochloroform solution. These solvent dependent effects on the dimethylamino proton signal form were not accompanied by other significant changes in spectra, and integration of spectra established that no carbon-bound proton in I*a* exchanged with deuterium oxide in deuterium oxide–deuterochloroform media, or had any exchange of carbon-bound proton for deuterium occurred in the preparation of the deuterochloride I*b*.

The dimethylamino protons of the sulfur trioxide compound I*c* appeared as two well-separated 3-proton singlets at 2.44 and 2.85 p.p.m., but the dimethylamino protons of the hydrogen sulfate I*d* appeared as a 6-proton broad signal.[1]

Proton spectra of II*a* were also characterized by a well-resolved doublet of doublets pattern centered at 2.79 and 3.12 p.p.m. (also reproduced at 40 Mc. at 2.73 and 3.10 p.p.m.). Equilibration of deuterochloroform solutions of II*a* with deuterium oxide again collapsed the dimethylamino proton doublet of doublets pattern to a sharp singlet, and integration of the spectra established that no carbon-bound proton in II*a* had exchanged with deuterium.

Concentration effects were observed in spectra of I*b* and II*a* in deuterochloroform, initial 15% solutions of both salts exhibiting singlet signals for the dimethylamino protons, which were split into doublet of doublets patterns, respectively, on 1:1 dilution with deuterochloroform.

The observed complexities of the N-methyl proton signals in I*a*, I*b*, I*c*, and II*a* must arise through magnetic nonequivalence on the 2 N-methyl groups in each case.[2] Thus, in I*a* and II*a* the 2 nonequivalent N-methyl groups appear as two 3-proton signals further split into a doublet of doublets pattern by coupling between the N-methyl protons and the ammonium proton.[3] The absence of an

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[1] Similar in appearance to the broad N-methyl signal of dimethyl-3-chloropropylammonium chloride (11).

[2] Temperature dependence and dilution effects in spectra of I*a*, I*b*, and II*a* deny spin–spin interactions as a reasonable basis for the observed multiplicities; also long-range coupling constants are generally smaller than the 5–6 c.p.s. (10 c.p.s. at dry ice temperatures) separations found.

[3] The field independence of the 5 c.p.s. spacings in the doublet of doublets pattern in I*a* and II*a* spectra as well as their magnitude support this assignment. Spin–spin interactions between N-methyl protons and an ammonium proton giving rise to coupling constants of 4.5–6.17 c.p.s. in various solvents have been observed (12–14).

TABLE I.—60 MC. PROTON SPECTRA OF METHADON DERIVATIVES AND ANALOGS[a]

Compd.	Acetyl Protons	Aromatic Protons	C_5- and C_6-Methylene/Methine Protons	C-Methyl Protons	*N*-Methyl Protons
I	3H: 0.84 (t), J = 7 2H: 2.27 (q), J = 7[b]	10H: 7.38 (m)	3H: 1.7–3.1 (m)	3H: 0.48 (d), J = 6	6H: 2.14
I*a*	3H: 0.83 (t), J = 7 2H: 2.27 (q), J = 7[b]	10H: 7.43 (m)	1H: 2.43 2H: 2.95–3.35 (m)	3H: 0.72 (d), J = 6.5	3H: 2.72 (d), J = 6 3H: 2.82 (d), J = 5
I*b*	3H: 0.83 (t), J = 7 2H: 2.27 (d), J = 7[b]	10H: 7.50 (m)	1H: 2.44 2H: 2.95–3.35 (m)	3H: 0.72 (d), J = 6.5	3H: 2.73[c] 3H: 2.83[c]
I*c*	3H: 0.86 (t), J = 7 2H: 2.16 (q), J = 7[b]	10H: 7.48 (m)	1H: 2.33 2H: 2.8–3.3 (m)	3H: 0.61 (d), J = 6.5	3H: 2.44 3H: 2.85
I*d*	3H: 0.80 (t), J = 7 2H: 2.20 (q), J = 7[b]	10H: 7.25 (m)	1H: 2.38 2H: 2.95–3.25 (m)	3H: 0.60 (d), J = 6.5	6H: 2.81 (b)
II*a*	3H: 0.76 (t), J = 7 2H: 1.7–2.8 (m)[d]	10H: 7.50 (m)	1H: 3.3–3.8 (m) 2H: 1.7–2.8 (m)[d]	3H: 1.25 (d), J = 6.5	3H: 2.79 (d), J = 5[c] 3H: 3.12 (d), J = 5[c]
III	3H: 0.81 (d), J = 6	10H: 7.30 (m)	[e]	3H: 0.74 (d), J = 6	6H: 2.18
IV	...	10H: 7.20 (m)	3H: 2.0–2.3 (m)	3H: 0.92 (d), J = 5.5	6H: 2.11
V	...	10H: 7.20–7.80 (m)	1H: 2.8 (m) 2H: 2.2–2.65 (m)	3H: 1.18 (d), J = 6.5	6H: 2.22

[a] Spectra were obtained on 15% (w/v) deuterochloroform solutions using a Varian Associates A-60 spectrometer. Chemical shifts (δ) are measured in p.p.m. downfield from an internal reference of tetramethylsilane. Data are recorded in order: chemical shift in p.p.m., multiplicity (in parenthesis), coupling constant in c.p.s. Signals are singlets except as noted. Abbreviations used are: b, broad; d, doublet; m, multiplet; t, triplet; q, quartet. [b] Fine splitting of about 1.5 c.p.s. was also observed. [c] Observed on 1:1 dilution of the initial 15% solution. [d] Two water protons are also observed in this range on 15% solutions. On 1:1 dilutions the water protons are consolidated as a 2 proton singlet at 2.42 p.p.m. The sample of II*a* used was a hydrochloride monohydrate (10). [e] Five unassigned protons appear: 1H, 1.88; 2H, 1.0–1.7 (m); 2H, 2.15–3.0 (m). A single proton geminal to hydroxyl is at 3.90 p.p.m. (q), J = 9.5 and 3.0 c.p.s. by first-order analysis.

ammonium proton in the deuterochloride I*b* simplified the *N*-methyl proton signals so that only a doublet is present. In the sulfur trioxide compound (I*c*) there likewise is no ammonium proton; however, in this instance the 2 *N*-methyl singlets are separated by 0.4 p.p.m.

The magnetic nonequivalence of the 2 *N*-methyl groups of these derivatives is not a consequence of restricted rotation about the N—C_6 bond. Such restricted rotation and consequent *N*-methyl nonequivalence occurs in *N*-methylamides (15), *N*-methylamidinium compounds (16), and in certain heterocyclic *N*-methyl compounds (17–19) where partial planar character of the nitrogen–carbon bond is involved. A very slow rate of amine inversion might be a basis for nonequivalence of the *N*-methyl protons, and some similarities exist between the present instance and spectra of dibenzylmethylammonium chloride (20) in aqueous acid. However, persistence of the nonequivalence of 60° does not support this explanation. Were slow inversion the case, however, some of the solvent effects could be readily understood as resulting from increased nitrogen inversion rates.

Of the conditions under which unexpected nonequivalence of protons obtain, as summarized by Bible (21), more favored explanation of the instant nonequivalence derives from inherent molecular asymmetry attributed to the nearby asymmetric carbon atom in the methadon and isomethadon molecules (C_6- and C_5-, respectively). This inherent asymmetry could manifest itself in nonequivalence of the *N*-methyl protons, of the C_5- or C_6-methylene protons, or of both sets of protons. The concept has been used to explain similar spectral complexity for other dimethylamino compounds (22, 23).

However, presence of dilution effects in the spectra of I*b* and II*a*, equivalence of the *N*-methyl protons of the related nitriles *dl*-4-dimethylamino-2,2-diphenylvaleronitrile hydrochloride (IV) and *dl* - 4 - dimethylamino - 3 - methyl - 2,2 - diphenylbutyronitrile hydrochloride (V), and identity of effect in both methadon (where the asymmetric C_6-carbon is 3 bonds separated from the *N*-methyl protons) and isomethadon (where the asymmetric C_5-carbon is 4 bonds separated), as measured by the coupling constants J = 5–6 c.p.s., suggest other factors may be involved. These several observations are consistent with a molecular asymmetry associated with a preferred conformation of the molecules I and II, the preferred conformation being formed through hydrogen bonding between cationic nitrogen and the carbonyl group as postulated by Beckett (2–4).

The dilution effects of the spectra of I*b* and II*a*, together with the simplification of spectra on equilibration with deuterium oxide suggest that the preferred conformations of the I and II molecules in solution giving rise to the magnetically nonequivalent *N*-methyl groups are not assumed in every instance of concentration and solvent choice, but that such asymmetric conformations may exist in special situations. Extension of these considerations to the complex media of living animals must therefore be done with caution.

The increased shielding (0.50 p.p.m.) of the C_6-methyl protons of I*a* in comparison with that of the C_5-methyl protons of II*a* may also be considered in terms of a preferred conformation of the molecules involving close approach of the carbonyl oxygen and the ammonium proton. In such conformation the C_5-methyl group of II*a* is very nearly in the plane of the C_4-benzene ring (using Dreiding models), whereas the C_6-methyl group of I*a* is more nearly above the plane of the C_4 benzene ring and thereby is subject to increased long-range diamagnetic shielding of the benzene ring.

The three C_5- and C_6-methylene and methine protons of I and II derivatives are magnetically nonequivalent. One proton appeared as a singlet overlapping the acetyl methylene quartet, and 2 protons appeared as a series of lines overlapping one another and/or the *N*-methyl signals. One of these latter

multiplets must be the C_6-proton (in I*a*), since it would be spin-spin coupled to the C-methyl protons, the ammonium proton, and probably one or both C_5-protons, and being adjacent to nitrogen, must be at low field. The other low field proton is then one of the C_5-methylene protons, the other being at higher field and overlapping the acetyl methylene quartet.

The nonequivalence of these methylene protons in I and II derivatives is most readily explained in terms of the nearby amsymmetric carbon atom C_6- and C_5,-, respectively (21), and in this matter, the precursor nitrile salts IV and V exhibit methylene proton nonequivalence also.

Attempts at further analysis of the methylene/methine proton signals on spectra of α-methadol (*dl* - α - 6 - dimethylamino - 4,4 - diphenylheptan-3-ol) (III) or of the nitrile precursors of I and II, IV and V, respectively, were thwarted by overlapping of these signals with one another and with those of the dimethylamino protons. It is to be noted that the dimethylamino proton signals in both nitriles IV and V fall in a high field relative to their ketone analogs I*a* and II*a*.

EXPERIMENTAL[4]

6 - Dimethylamino - 4,4 - diphenylheptan - 3-one Deuterochloride (Ib).—Ten grams of commercial methadon hydrochloride was recrystallized 3 times from 99.8% deuterium oxide (Stuart Oxygen Co., San Francisco, Calif.) to constant melting point, m.p. 232–234°.

6 - Dimethylamino - 4,4 - diphenylheptan - 3 - one Sulfur Trioxide Compound (Ic).[5]—A mixture of 1.5 Gm. of I*a*, 1.8 ml. of isopropenyl acetate, and 2 drops of concentrated sulfuric acid was distilled slowly over a 7-hr. period. The mixture was filtered from insoluble material (0.32 Gm. of recovered I*a*, m.p. 230–234°), and the filtrate was concentrated. A red resinous precipitate formed and crystallized over several weeks, yielding 0.37 Gm. of product I*c*. Recrystallization from benzene gave crystals, m.p. 139.0–141.0°, and from ethanol–ether gave the analytical sample, m.p. 140.0–142.5°. $\lambda_{max.}$ 255 mμ (ϵ 579, inflection), 260 mμ (ϵ 646), 266 mμ (ϵ 629), 292 mμ (ϵ 624); $\lambda_{min.}$ 250 mμ (ϵ 526), 264 mμ (ϵ 624), 277.5 mμ (ϵ 502).

Anal.—Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.59; S, 8.23. Found: C, 64.89; H, 6.98; N, 3.57; S, 8.54.

6 - Dimethylamino - 4,4 - diphenylheptan - 3 - one Hydrogen Sulfate (Id).—A solution of 1.0 Gm. of methadon in absolute ethanol was treated with an ethanolic sulfuric acid solution. The solution was evaporated under vacuum and the oily residue was crystallized from chloroform–ether, yielding 0.30 Gm. of salt, m.p. 147.0–149.0°. An additional 0.21 Gm., m.p. 144.0–146.5°, was recovered from the filtrate. After further recrystallizations from methanol–ether and from ethanol–ether, the salt melted at 146.0–148.0°.

Anal.—Calcd. for $C_{21}H_{27}NO.H_2SO_4$: N, 3.44; S, 7.87. Found: N, 3.39; S, 8.13.

[4] Melting points were determined using a calibrated thermometer and a heated oil bath. Ultraviolet light absorption spectra were recorded on methanol solutions using a Beckman model DU spectrophotometer.

[5] The minor by-product I*c* was obtained in otherwise unsuccessful attempts at enolacetylation of I*a*. The structure of I*c* as a sulfur trioxide derivative of I is supported by elemental analysis, ultraviolet light absorption essentially identical with spectra of I*a* (8), water solubility (from which water solutions barium chloride precipitated barium sulfate), and nonidentity with the hydrogen sulfate salt I*d* prepared with sulfuric acid in the usual way.

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