the guanidino group[6] exhibited heterogeneity at about *p*H 5 and remained monodispersed at *p*H 6.5. The appearance of heterogeneity in both of these albumin derivatives was found to be reversible.[7]

Further work is being done on this problem in the intermediate *p*H range of 4 to 11.

In view of these heterogeneity effects, some of which also have been observed by Reichmann and Charlwood,[8] it would seem questionable as to whether one could make an unambiguous statement about the configuration of albumin at low and high *p*H. It is, therefore, not yet possible to decide whether the anomalous reactivity of serum albumin at low and high *p*H can be attributed either to expansion of the molecule[2] or to reversible formation and breakage of internal hydrogen bonds.[9] It may be that both effects are present.

[6] W. L. Hughes, Jr., H. A. Saroff and A. L. Carney, This Journal, **71**, 2476 (1949).

[7] The sedimentation studies on the guanidinated albumin were made several years ago by H. A. Saroff while at the Department of Physical Chemistry, Harvard Medical School.

[8] M. E. Reichmann and P. A. Charlwood, *Can. J. Chem.*, **32**, 1092 (1954).

[9] M. Laskowski, Jr., and H. A. Scheraga, This Journal, **76**, 6305 (1954).

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A Mechanical Resolution of *dl*-Methadone Base

BY HAROLD E. ZAUGG

RECEIVED DECEMBER 23, 1954

The potent analgesic *l*-methadone has been separated from its much less active optical antipode by a number of workers. Crystallization of the diastereoisomeric acid *d*-tartrates from acetone[1] and *n*-propyl alcohol[2] leads to the preferential deposition of *l*-methadone *d*-tartrate. A cleaner separation is obtained with *d*-α-bromocamphor-π-sulfonic acid which forms a water-insoluble salt with *d*-methadone and a water-soluble one with the *l*-form.[3]

This note reports a successful resolution of *dl*-methadone by slow crystallization of the base from a concentrated petroleum ether solution seeded with two crystals of the pure *d*-base and two crystals of the pure *l*-base, both obtained in the conventional manner by preliminary resolution through the acid *d*-tartrates. Nearly 50% of the original *dl*-mixture was recovered in the form of four crystals (one weighed 11 g.), far from physically perfect, but of optical purity equal to that of the seeds from which they were grown.

Experimental

The apparatus consisted of a cylindrical glass jar 90 mm. in diameter with straight sides 80 mm. high fitted with a metal screw cap (neither lined nor gasketed) in the center of which a round hole was cut to accommodate a no. 4 rubber stopper. A glass tube (8 mm. inside diameter), extending through the stopper, was equipped with a silicone lubricated rubber seal which served as a bearing for the stirrer. The stirrer was made of a 5-mm. glass rod bent at a point just below the end of the bearing tube so that the resulting radius of eccentricity of the rotating stirrer was approximately half the radius of the cylindrical container.

Fifty-six grams of *dl*-methadone base was dissolved in 225 cc. of boiling petroleum ether (b.p. 63–68°, Skellysolve B) and filtered by gravity into the open cylindrical jar. The solution was concentrated on the steam-bath to a volume of 145 cc. The metal cap with the stirrer inserted was then screwed to the top of the jar which was placed in an oven held at 40°. During the cooling process stirring at 240–250 r.p.m. was accomplished by means of a constant speed stirring motor placed above the oven and attached to the stirrer shaft extending through the oven vent. (A temperature-controlled water-bath probably could be substituted for the oven, with the result that observational conditions of the experiment would be greatly improved.)

When temperature equilibrium was attained, the cap was removed and two seeds each of pure *d*- and *l*-methadone base were placed in alternating order around the perimeter of the container bottom, so that seeds of like sign were directly opposite each other. The seeds used were approximately 2–3 mm. across and were taken, still wet with solvent, directly out of the petroleum ether (Skellysolve B) solution from which they had been freshly crystallized. The screw cap was replaced and stirring was resumed at the same rate as before and was continued at 40° for 125 hours. During this time approximately one-fourth of the solvent evaporated through the threads of the screw cap and two large and two smaller crystals grew from the original seeds. The two crystals of *l*-methadone weighed 8.8 g. ($[\alpha]^{25}\mathrm{D}$ $-35.7°$, *c* 4, Skellysolve B) and 4.2 g. ($[\alpha]^{26}\mathrm{D}$ $-36.2°$, *c* 4, Skellysolve B). The two crystals of *d*-methadone weighed 11.2 g. and 1.9 g. (combined $[\alpha]^{25}\mathrm{D}$ $+ 36.0°$, *c* 4, Skellysolve B). The total of 26.1 g. of resolved material represents a 46% yield, but 29.0 g. of *dl*-methadone was obtained from the residual solution to give a nearly quantitative recovery of product.

The optical purity of the resolved material was further tested by grinding together the two crystals of like sign and measuring the rotation of a solution in absolute ethanol: *l*-form, $[\alpha]^{27}\mathrm{D}$ $-26.8°$ (*c* 4.10, *l* 2 dcm.); *d*-form, $[\alpha]^{27}\mathrm{D}$ $+26.5°$ (*c* 4.00, *l* 2 dcm.).

Brode and Hill[1] reported the values $[\alpha]^{22}\mathrm{D}$ $-29.91°$ (*c* 2.66, *l* 2 dcm., absolute ethanol) for *l*-methadone base and $[\alpha]^{26}\mathrm{D}$ $+29.51°$ (ethanol) for the *d*-form. Larsen and coworkers[2] reported the values $[\alpha]^{25}\mathrm{D}$ $-26°$ and $+26°$ (*c* 1.5, U.S.P. ethanol) for *l*- and *d*-methadone, respectively. Walton, Ofner and Thorp[4] reported the values $[\alpha]^{22}\mathrm{D}$ $-32°$ (alcohol) and $[\alpha]^{20}\mathrm{D}$ $+28°$ (alcohol) for the two optical isomers of methadone.

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[1] W. R. Brode and M. W. Hill, *J. Org. Chem.*, **13**, 191 (1948).

[2] A. A. Larsen, B. F. Tullar, B. Elpern and J. S. Buck, This Journal, **70**, 4194 (1948).

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Substituted Malononitriles of the Type Aryl $CH_2CX(CN)_2$

BY J. C. WESTFAHL AND T. L. GRESHAM

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Recent work in this Laboratory has made available a series of monosubstituted malononitriles of the type Aryl $CH_2CH(CN)_2$.[1] This paper reports some of the results of a study of these compounds.

In agreement with the observations of Hessler,[2] benzylmalononitrile (I) and in general Aryl $CH_2CH(CN)_2$ were soluble in aqueous sodium hydroxide, and when precipitated promptly by the addition of a mineral acid were recovered unchanged.

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[1] J. C. Westfahl and T. L. Gresham, This Journal, **76**, 1076 (1954).

[2] J. C. Hessler, *Am. Chem. J.*, **22**, 181 (1899)

TABLE I

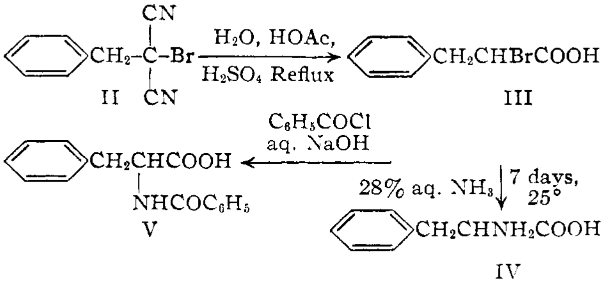
PREPARATION OF ARYL $CH_2CX(CN)_2$

Aryl	X	Yield, % (m.p., °C.)	M.p., °C. (pure)	Analyses, %							
				Calculated				Found			
				C	H	N	X	C	H	N	X
Phenyl	Cl	48.1 (89–91)	90–91	63.00	3.70	14.70	18.60	63.09 63.14	3.80 3.77	14.61	18.61 18.66
Phenyl	Br	60.8 (115–119)	119.5–120.5[a]	51.08	3.00	11.92	34.00	51.24 51.26	2.93 3.00	11.92	34.13[b] 34.21
Mesityl	Cl	84.3 (63–65.3)	66.3–67.3	67.09	5.63	12.04	15.24	67.08 67.07	5.54 5.63	12.07	15.18
Mesityl	Br	84.6 (85–91)	95.5–96.5	56.33	4.72	10.11	28.82	56.39 56.47	4.60 4.75	10.00	28.92[b] 29.03
p-Methoxyphenyl	Br	43.8 (54–57.5)	59.5–60.5	49.83	3.42	10.57	30.15	50.09 49.92	3.42 3.39	10.62	30.56[b] 30.29
2,5-Dimethoxyphenyl	Cl	85.1 (51–52.3)	51.5–52.5	57.49	4.42	11.18	14.14	57.36 57.40	4.44 4.43	11.20	13.67

[a] Reference 3. [b] Determined by dissolving sample in glacial acetic acid, adding KI solution and titrating liberated iodine with standard thiosulfate.

If such a basic solution of Aryl $CH_2CH(CN)_2$ was allowed to stand at room temperature, hydration and hydrolysis of nitrile groups occurred rapidly. When a freshly prepared solution of I in aqueous sodium hydroxide was poured rapidly into a stirred, cold solution of sodium hypobromite an immediate precipitation of benzylbromomalononitrile (II) occurred. Pure II melted at 119.5–120.5°. Hessler[3] prepared II by the action of an ether solution of bromine on the dry sodium salt of I. He obtained II of m.p. 119–120°. The structure of II was confirmed as shown in Chart 1.

CHART 1



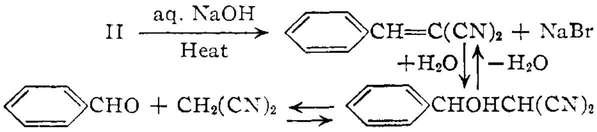
dl-Phenylalanine (IV) was identified by its decomposition temperature, by comparison of the microscopic appearance of its crystals with published[4] photomicrographs of *dl*-phenylalanine, and by the melting point of its benzoyl derivative V.

The reaction of freshly prepared aqueous basic solutions of Aryl $CH_2CH(CN)_2$ with cold aqueous solutions of sodium hypochlorite or sodium hypobromite gave the series of compounds shown in Table I.

These solids were insoluble in water and aqueous base and were soluble in most organic solvents. When allowed to stand in water at room temperature the odor of hypohalous acid was evident. Addition of the solids to aqueous potassium iodide solutions containing acetic acid caused the liberation of iodine either at room temperature or on slight warming. Because of the similarity to II in the method of preparation and in the properties of these compounds, they are assumed to have the structure Aryl $CH_2CX(CN)_2$ where X is chlorine or bromine. When an aqueous, basic solution of I was added to a cold, stirred aqueous solution of sodium hypoiodite, solid failed to separate.

By steam distilling a suspension of II in aqueous sodium hydroxide, benzaldehyde was obtained.[5] This decomposition probably proceeds as shown in Chart 2.

CHART 2



Because of the positive character of the halogen in Aryl $CH_2CX(CN)_2$ the possibility that they might act as allyl halogenating agents was considered. Refluxing II, benzoyl peroxide and cyclohexene in carbon tetrachloride gave a low yield of 3-bromocyclohexene.

Experimental[6]

The preparation of only one chloro compound and one bromo compound will be described since the procedures used for the compounds listed in Table I were similar.

2,5-Dimethoxybenzylchloromalononitrile.—To a stirred solution of 262 g. (0.185 mole) of 5.25% sodium hypochlorite (commercial household bleach) cooled in an ice–salt-bath was added a solution prepared from 18.5 g. (0.46 mole) of sodium hydroxide, 185 ml. of distilled water and 20.00 g. (0.093 mole) of 2,5-dimethoxybenzylmalononitrile. The nitrile solution was prepared by cooling the sodium hydroxide solution in an ice-bath, adding the 2,5-dimethoxybenzylmalononitrile, and rapidly stirring and warming the mixture. At 19° nearly all of the solid was dissolved. The mixture was filtered rapidly through a funnel containing glass wool. The filtrate ran into the vigorously stirred, cold (−7°) sodium hypochlorite solution. The product, which separated immediately, was a pale yellow solid. After stirring for one minute, an equal volume of cold water was added and the slurry was filtered with suction. The solid was washed with cold water and dried *in vacuo* (<30°) to give 20.04 g. (85.1%) of pale yellow 2,5-dimethoxybenzylchloromalononitrile of m.p. 51–52.3°. Recrystallization from hexane–benzene gave nearly colorless crystals of m.p. 51.5–52.5°.

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(3) Reference 2, p. 192.

(4) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," Charles C Thomas, Springfield, Ill., 1938, p. 490.

(5) According to Hessler, II . . . "is not affected by aqueous sodium hydroxide"; reference 2, p. 193.

(6) All melting points and boiling points are uncorrected.

Benzylbromomalononitrile (II).—A sodium hypobromite solution was prepared by adding 1.8 ml. (5.1 g., 0.032 mole) of bromine dropwise to a stirred, cold sodium hydroxide solution prepared from 3.85 g. (0.096 mole) of sodium hydroxide and 45 ml. of water. The nitrile solution was prepared by adding 5.00 g. (0.032 mole) of benzylmalononitrile (I) to a cold solution prepared from 5.0 g. (0.13 mole) of sodium hydroxide and 50 ml. of water. The mixture was stirred and warmed in a hot water-bath until compound I was dissolved. The nitrile solution was poured rapidly into the stirred, cold hypobromite solution. The precipitated yellow solid was filtered with suction, washed with cold water and dried to constant weight in air at room temperature to give 4.57 g. (60.8%) of yellow II of m.p. 115–119°. One recrystallization from benzene–hexane gave 3.29 g. (43.8%) of nearly colorless II of m.p. 119.5–120.5°.

Hydrolysis of II.—A mixture of 2.00 g. (8.5 millimoles) of II, 4.0 ml. (73.5 millimoles) of concentrated sulfuric acid, 20 ml. of glacial acetic acid and 10 ml. of water was refluxed for 16 hours. The solution was poured into 150 ml. of water and the mixture was extracted four times with benzene. The benzene extract was washed once with water and then extracted twice with a saturated aqueous sodium bicarbonate solution. After washing the combined bicarbonate extract once with ether, it was acidified with hydrochloric acid and the insoluble liquid, III, was taken up in ether and the aqueous layer extracted once with ether. After drying with magnesium sulfate, the combined ether solution was freed of ether to leave 1.81 g. (92.8%) of crude III.

***dl*-Phenylalanine (IV).**[7]—Crude III, 1.81 g. (*ca.* 7.9 millimoles) and 25 ml. (0.37 mole) of 28% aqueous ammonia were stored in a closed flask at room temperature for one week. The light yellow solution was evaporated *in vacuo* at 50° until solid began to separate. The *p*H was adjusted to between 6 and 7 with dilute hydrochloric acid and the mixture was cooled in ice. The solid was filtered with suction and dried to give 0.76 g. (58%) of crude IV. The crude IV was recrystallized from ethanol–water to give colorless plates.[4] After filtering, washing with ethanol and drying, the solid weighed 0.57 g. (43.5%) and had a decomposition temperature of 275°. Authentic *dl*-phenylalanine decomposed at 275° under the same conditions.

Benzoylation of recrystallized IV was carried out by shaking 0.50 g. (3.0 millimoles) of IV, 25.4 ml. of water, 0.254 g. (6.35 millimoles) of sodium hydroxide and 0.35 ml. (0.43 g., 3.06 millimoles) of benzoyl chloride until the odor of benzoyl chloride disappeared. Acidification of the solution gave crude V of m.p. 182.5–185° which was purified by one recrystallization from water–ethanol to give crystals of m.p. 186.5–187.5°; reported m.p. 188°.[8] The m.p. of a mixture of V and authentic N-benzoyl-*dl*-phenylalanine was not depressed.

Alkaline Degradation of II.—A suspension of II in aqueous base was prepared from 1.56 g. (10.0 millimoles) of I, 1.2 g. (30 millimoles) of sodium hydroxide, 0.55 ml. (1.60 g., 10 millimoles) of bromine and 15 ml. of water as given for the preparation of II. The resulting suspension of II in aqueous base was steam distilled until insoluble liquid no longer distilled. The steam distillate was made weakly acid and was extracted twice with ether. After drying with magnesium sulfate, the magnesium sulfate was filtered and the ether was removed to leave 0.17 g. (16% from I) of crude benzaldehyde. When a solution of the crude benzaldehyde (*ca.* 1.6 millimoles) in 5 ml. of ethanol was added to an aqueous solution prepared from 0.46 g. (3.2 millimoles) of phenylhydrazine hydrochloride, 0.26 g. (3.2 millimoles) of sodium acetate and 5 ml. of water, a precipitate of the phenylhydrazone separated immediately. After heating to boiling, the mixture was cooled in ice and filtered. The crude derivative had m.p. 150–154°. After two recrystallizations from ethanol–water the m.p. was 154–155°. The reported m.p. of benzaldehyde phenylhydrazone is 156.[9] The identity of the benzaldehyde was confirmed by dividing the ethanol solution from a similar degradation into two parts and preparing the semicarbazone (m.p. 214.5–215.5°, reported m.p. 214°[9]) and 2,4-dinitrophenylhydrazone (m.p. 235–235.8°, reported m.p. 237°[9]).

A similar experiment starting with *p*-methoxybenzylmalononitrile gave anisaldehyde (15.4% crude). The 2,4-dinitrophenylhydrazone had m.p. 257–259°. The reported m.p. of anisaldehyde 2,4-dinitrophenylhydrazone is 254°.[9]

3-Bromocyclohexene.—A mixture of 0.73 g. (3.1 millimoles) of II, 1.6 ml. (1.3 g., 16 millimoles) of cyclohexene of b.p. 80.5–81° (730.7 mm.) and $n^{23.5}_D$ 1.4450, 34.4 mg. (0.14 millimole) of benzoyl peroxide and 7 ml. of carbon tetrachloride was refluxed for 12 hours and 45 minutes. The carbon tetrachloride, excess cyclohexene and 3-bromocyclohexene were removed from the reaction mixture at 0.05 mm. and 50°. The carbon tetrachloride and cyclohexene were separated from the 3-bromocyclohexene by distilling at 130 mm. and a final pot temperature of 50°. The residue of crude 3-bromocyclohexene was evaporatively distilled at 0.05 mm. to give 0.11 g. of colorless liquid. Quantitative measurements of the infrared absorption spectrum of this liquid and of the spectrum of pure 3-bromocyclohexene, prepared by the method of Ziegler, *et al.*,[10] permitted the 3-bromocyclohexene content of the liquid to be calculated. Based on measurements of the peak at 19.4 μ (KBr prism) the liquid contained 54.6 ± 2% of 3-bromocyclohexene or a 12 ± 2% yield of pure 3-bromocyclohexene based on II.

Acknowledgment.—The authors are indebted to J. R. Kubik and A. K. Kuder for the analyses and to J. J. Shipman for the determination and interpretation of infrared spectra.

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α-Reduction of a Steroidal Δ^{16}-20-Ketone with Lithium Aluminum Hydride

BY ELLIOT L. SHAPIRO, DAVID GOULD AND E. B. HERSHBERG

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It has generally been observed that reduction of steroidal 20-ketones by means of catalytic hydrogenation, or lithium aluminum hydride, proceeds to give 20β-hydroxy compounds as the major products.[1] Indeed when there is substitution at C-17, the formation of the β-hydroxyl configuration generally proceeds almost quantitatively.[2] Heretofore, 20α-hydroxypregnanes have been obtained as the major product only in procedures such as that of Ercoli, who used zinc and acetic acid to obtain a 20α- and 20β-mixture of 5,16-pregnadiene-3β,20-diols from 5,16-pregnadien-3β-ol-20-one acetate.[3] Reduction to the 20β-configuration has been observed so generally that Romo, *et al.*, assumed that the treatment of 7,16-allopregnadien-3β-ol-20-one acetate with lithium aluminum hydride led to the corresponding 20β-hydroxy compound.[4] Our results, using a Δ^{16}-20-ketopregnene, however, show that it is also possible to obtain 20α-hydroxyl groups by reduction with this reagent.

When we treated 5,16-pregnadien-3β-ol-20-one

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