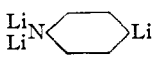
TABLE I

REACTIONS OF RX COMPOUNDS WITH n-C_4H_9Li

RX	RX, mole	Ether, cc.	n-C_4H_9Li, mole	Ether, cc.	Reaction time, min.	Product[a]	Yield, %
o-$BrC_6H_4NH_2$	0.042	25	0.128	125	45	Sulfonamide	40
p-$BrC_6H_4NH_2$	.033	25	.10	100	60	Sulfonamide	65
p-$BrC_6H_4NHCH_3$[b]	.063	25	.13	150	60	Acid[c]	27
N-p-$IC_6H_4(CO)_2C_6H_4$[d]	.03	0[e]	.03	250	60	Acid	37

[a] See general procedure. [b] Prepared in essential accordance with the procedure of Chowdhury, Desai and Hunter, *J. Indian Chem. Soc.*, 10, 637 (1933). [c] Identified by mixed melting point with an authentic specimen. Houben and Shottmueller, *Ber.*, 42, 3739 (1909). [d] Prepared by the method of Gabriel, *Ber.*, 11, 2260 (1878). [e] RX was added in the solid state to the solution of n-C_4H_9Li.

lithium with p-bromoaniline[2a] has now been more carefully examined. In this reaction there is formed a bright yellow precipitate which has been isolated and analyzed. It appears to be p-N,N-trilithioaniline (A).



(A)

This product, when dry, is highly explosive in contact with air. When less than two equivalents of n-butyllithium were used, or when the reaction mixture was extremely dilute, no precipitate formed and no p-aminobenzoic acid could be isolated after carbonation of the reaction mixture.

Experimental

General Procedure.—An ether solution of n-butyllithium, standardized by the indirect procedure,[3] was added to the RX compound dissolved in ether. In the experiments with o- and p-bromoaniline, approximately one-third of the RLi solution was added at such a rate that gentle refluxing was maintained. The heat of reaction then subsided and the remainder of the solution was added rapidly. With p-bromo-N-methylaniline one-half of the solution was added dropwise and the remainder rapidly. All of the interconversions were carried out at room temperature with the exception of the one with N-(p-iodophenyl)-phthalimide. The latter was run at −50°. The reaction times given in the accompanying table apply to the period of time after the addition of RLi solution was completed. All reaction mixtures were poured on a suspension of crushed, dry carbon dioxide in ether and then hydrolyzed with water. The acid produced was isolated by acidifying the aqueous alkaline layer of the hydrolyzed mixture or by treating the aqueous alkaline layer with benzenesulfonyl chloride and then precipitating the benzenesulfonamide of the amino acid with dilute hydrochloric acid. Details are given in Table I.

p-N,N-Trilithioaniline.—An ether solution of n-butyllithium was added to p-bromoaniline as described in the preceding section. The yellow precipitate was collected under nitrogen, on a sintered-glass disc sealed into a previously tared weighing bulb. The weighing tube was swept with a warm current of nitrogen until it came to constant weight. The dried precipitate was slowly hydrolyzed with moist ether and finally with water. The ether layer was separated and dried over anhydrous sodium sulfate and fractionated. The aniline fraction was identified as acetanilide. The aqueous layer was titrated with 0.5 N hydrochloric acid. Aniline and lithium hydroxide were present in a 1 to 3 molar ratio. The yield of dry p-N,N-trilithioaniline was 70%.[4]

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(3) Gilman and Haubein, THIS JOURNAL, 66, 1515 (1944).

(4) The authors are grateful to R. K. Abbott for assistance.

The Influence of the Walls of the Autoclaves Upon the Hydrogenation of p-Cymene

BY V. N. IPATIEFF, HERMAN PINES AND E. E. MEISINGER

During the study of hydrogenolysis of polycyclic compounds in the presence of a copper–alumina catalyst[1] (67% CuO, 33% Al_2O_3) it was noticed that the degree of hydrogenolysis depended upon the autoclave used; a stainless steel autoclave caused much more hydrogen to be absorbed than an ordinary steel autoclave. In order to investigate the effect of ordinary and stainless steel autoclaves upon hydrogenation, p-cymene was subjected to the treatment with hydrogen in the presence of a copper–alumina catalyst.

The reaction was carried out in rotating autoclaves of 450-cc. capacity charged with 60 g. of p-cymene and with 6 g. of the above-mentioned CuO–Al_2O_3 catalyst which were heated at 325° for five hours in the presence of hydrogen at an initial pressure of 100 atmospheres. The percentage of p-cymene in the product was determined by ultraviolet absorption based on the band at 273.5 mμ equivalent.

In the absence of the catalyst no reaction took place irrespective of the material with which the autoclave was lined. In the presence of the catalyst there was formed (a) in the steel autoclave 2% of p-menthane; (b) in the stainless steel autoclave[2] 48% of p-menthane and 10% of lower boiling aromatics; (c) in the steel autoclave with a new stainless steel liner 21% of p-menthane and 2% of lower boiling aromatics.

The results with the newly machined stainless steel liner showed that the promoting effect could have only been in part due to any contamination present in the old stainless steel autoclave where the largest percentage of p-menthane was formed. The most probable explanation of these results is that the stainless steel is responsible for all of the promoting effect, the greater activity of the old stainless steel autoclave as compared with the autoclave with the new steel liner being due to

(1) V. N. Ipatieff and V. Haensel, THIS JOURNAL, 64,520 (1942).

(2) The following is the composition of the steel as recorded by the manufacturer: The ordinary steel bomb was made of 1020 steel which contained carbon, 0.15–0.25%; manganese, 0.30–0.60%; phosphorus, 0.045% max.; sulfur, 0.50% min. The stainless steel bomb was made of type 304 grade 18-8 which contained carbon, 0.08%; manganese, 2.00%; silicon, 0.5% max.; chromium, 18–20%; nickel, 8–10%.

the etching of the surface of the old autoclave and the consequent greater exposure of the active constituent of the stainless steel. This active constituent might well have been the nickel present in relatively large amounts therein.

The above experiments therefore demonstrate that in a high-temperature hydrogenation it is important to indicate the nature of the steel of which the bomb is made.

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Resolution of *dl*-Methadone and *dl*-Isomethadone

BY E. E. HOWE AND MEYER SLETZINGER

Recently Larsen, *et al.*,[1] have reported practical methods for the resolution of *dl*-methadone, 6-methylamino-4,4-diphenylheptanone-3 and of *dl*-isomethadone, 6-dimethylamino-5-methyl-4,4-diphenylhepanone-3 with *d*-tartaric acid. We, too, have investigated this problem and inasmuch as our approach has differed in some respects from those of other workers we wish to report briefly on our observations.

d-Methadone forms an easily-purified, water-insoluble *d*-α-bromocamphor-π-sulfonate from which the pure *d*-isomer is readily prepared. l-Methadone *d*-tartrate may then be obtained from methadone residues derived from the mother liquors in a state of such high purity that no recrystallization is necessary. Should only the active *l*-form be desired the *d*-isomer may be conveniently removed from a butyl alcohol solution as the *p*-nitrobenzoyl-L-glutamate. The latter salt, however, does not readily lend itself to purification.

When a solution of *dl*-isomethadone in isopropyl alcohol is heated with *p*-nitrobenzoyl-L-glutamic acid the salt of the *d*-isomer separates and can be obtained in the pure state. The enantiomorph may be isolated from the mother liquors.

To our knowledge this is the first reported use of *p*-nitrobenzoyl-L-glutamic acid as a resolving agent.

Experimental

d-**Methadone.**—Ten grams (0.029 mole) of *dl*-methadone hydrochloride and 5 g. (0.015 mole) of ammonium *d*-α-bromocamphor-π-sulfonate were dissolved in 25 cc. of hot 80% ethanol. The solution was cooled and the impure *d*-methadone salt was precipitated by the slow addition of 220 cc. of water. The mixture was chilled overnight and filtered. The collected salt was washed twice with ice-water and dried at 45°. It is important that the greater portion of the moisture be removed during the filtration step since the wet salt melts at 45°. The yield was 7.6 g. (85.0%), m. p. 125–127°.

The crude *d*-methadone bromocamphor sulfonate was dissolved in 10 cc. of ethanol and precipitated with 60 cc. of water. There was recovered 6.5 g. (85.5%) of product melting at 135–138°. This salt by conventional methods was converted in 95% yield to *d*-methadone hydrochloride; m. p. 243–244°; $[\alpha]^{23}D$ 1% in aqueous solution (+127.0°).

Anal. Calcd. for $C_{21}H_{28}ONCl$: C, 72.91; H, 8.16. Found: C, 72.90; H, 8.36.

l-**Methadone.**—All mother liquors and washes from the preparation of *d*-methadone-*d*-α-bromocamphor-π-sulfonate were combined and treated with 5 cc. of 40% sodium hydroxide solution. The methadone precipitated immediately and after chilling overnight was collected, washed twice with water and dried. This product and 2.4 g. of *d*-tartaric acid were dissolved in 35 cc. of *n*-butanol by heating to boiling. The solution was cooled and seeded with *l*-methadone-*d*-tartrate whereupon crystallization occurred. After two hours at room temperature 35 cc. of petroleum ether was added. The mixture was refrigerated overnight, was filtered and the collected salt was washed first with 1:1 butanol–petroleum ether and then with petroleum ether. The yield was 5.9 g. of *l*-methadone-*d*-tartrate (86.5%) melting at 149–150°. By successive treatment with sodium hydroxide and hydrochloric acid this salt was converted in 92% yield to *l*-methadone hydrochloride, m. p. 237–239°; $[\alpha]^{23}D$ (1% in aqueous solution) −127.0°.

Anal. Calcd. for $C_{21}H_{28}ONCl$: C, 72.91; H, 8.16. Found: C, 72.95; H, 7.99.

d-**Isomethadone** *p*-**Nitrobenzoyl-L-glutamate.**—A mixture of 105 g. (0.32 mole) of isomethadone base and 59.5 g. (0.18 mole) of *p*-nitrobenzoyl-L-glutamic acid in 595 cc. of isopropyl alcohol was boiled under reflux until solution was completed. The solution was allowed to cool to room temperature with stirring. The mixture was filtered and the crystalline product was washed with 20 cc. of cold isopropyl alcohol and then with ether. The yield was 73 g.; m. p. 168–171°. Recrystallization from isopropyl alcohol raised the melting point to 171–172°; $[\alpha]^{25}D$ (1% in methanol) +60°.

d-**Isomethadone Hydrochloride Monohydrate.**—A mixture of 73 g. of *d*-isomethadone-*p*-nitrobenzoyl-L-glutamate dissolved in 74 cc. of water and 44 cc. of chloroform was made alkaline with 130 cc. of 30% sodium hydroxide. After vigorous agitation of the mixture, the lower chloroform layer was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The oily residue was dissolved in 33 cc. of isopropyl alcohol and made acidic with 32.5 cc. of 4.9 *N* hydrochloric acid in isopropyl alcohol. Ethyl ether (256 cc.) was added and the white precipitate was filtered, washed with 50 cc. of isopropyl alcohol–ether solution (1:8) and dried at room temperature. The yield was 24 g. (38.9%), m. p. 173–174°; $[\alpha]^{25}D$ (1% in methanol) +90°. This substance analyzed correctly for a monohydrate.

Anal. Calcd. for $C_{21}H_{28}ONCl \cdot H_2O$: C, 69.28; H, 8.31; N, 3.84. Found: C, 69.55; H, 8.28; N, 4.03.

l-**Isomethadone Hydrochloride Monohydrate.**—The isopropyl alcohol mother liquors from the preparation of *d*-isomethadone-*p*-nitrobenzoyl-L-glutamate were evaporated to dryness *in vacuo*. The residue was dissolved in 140 cc. of water, then 140 cc. of chloroform was added. The mixture was made basic with 140 cc. of 30% sodium hydroxide and the chloroform layer was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The oily residue was dissolved in 70 cc. of isopropyl alcohol and treated with 70 cc. of 4.9 *N* hydrochloric acid in isopropyl alcohol. One liter of ether was added and the white precipitate was filtered, washed with 25 cc. of isopropyl alcohol–ether (1:8) and dried at room temperature. The yield was 31 g.; m. p. 170–172°.

Recrystallization by dissolving in 80 cc. of isopropyl alcohol and precipitating with 325 cc. of ether yielded 26.5 g.; m. p. 173–174°; $[\alpha]^{25}D$ (1% in methanol) −90°. This substance analyzed correctly for a monohydrate.

Anal. Calcd. for $C_{21}H_{28}ONCl \cdot H_2O$: C, 69.28; H, 8.31; N, 3.84. Found: C, 69.52; H, 8.08; N, 3.91.

(1) A. A. Larsen, B. F. Tullar, B. Elpern and J. S. Buck, THIS JOURNAL, **70**, 4194 (1948).