Experimental

Isomerization Experiments.—All operations involving addition of reactants to the reaction tube or removal of products from the reaction tube were carried out using a high vacuum technique.[7] Particular care was taken to remove all air from the hydrocarbon by repeated fractionation before distilling it into the reaction tube.

After all reactants had been introduced, the reaction tube was sealed off from the vacuum line and stored in a Dry Ice–acetone-bath. With the exception of the actual irradiation period, all reaction tubes were kept in Dry Ice–acetone-baths until the products were removed. This precaution was taken to prevent the possibility of some reaction occurring as might be the case if the samples were allowed to stand for several days at room temperature. The irradiations were carried out in a Co^{60} source at the Argonne National Laboratories.[8]

After irradiations, the reaction tube again was attached to the vacuum line and the break-off ruptured. All gases non-condensable at −78° were then removed by means of a Toepler pump and collected over mercury in a small thimble. A bead of potassium hydroxide on a platinum wire was introduced into the sample to remove any hydrogen bromide present. The thimble then was transferred to a Blacet–Leighton apparatus where the volume of the gas was measured. An aliquot was then measured out for analysis in the mass spectrometer.[9]

The liquid contents of the reaction tube were distilled out, washed with 10% potassium carbonate, followed by water, then dried over calcium chloride. The composition of the reaction product was determined by means of infrared analysis. A Beckman IR-2T spectrophotometer was used for the preliminary runs, while a Baird model AB2 spectrophotometer was used for the rest of the analyses. Calculations were based on the data observed at 7.98, 8.82, 8.62 and 10.30 μ.

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(7) H. Pines and R. C. Wackher, THIS JOURNAL, **68**, 595 (1946).

(8) The authors are indebted to Dr. Edwin J. Hart and Miss D. P. Walsh for their coöperation in making the irradiations.

(9) The authors are indebted to Dr. D. F. Mason for performing the mass spectral analyses.

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Preparation of α-*d*- and α-*l*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane

BY A. POHLAND AND H. R. SULLIVAN

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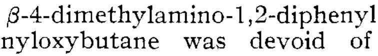
A number of esters of 4-dialkylamino-1,2-diphenyl-2-butanols have been reported to possess a high order of analgesic activity in animals.[1] One of these esters, α-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane (I), has been found to be an effective analgesic in humans.[2]



$$\begin{matrix} C_6H_5 \diagdown & & \diagup OCOC_2H_5 \\ & C & \\ C_6H_5CH_2 \diagup & & \diagdown CH(CH_3)CH_2N(CH_3)_2 \end{matrix}$$

I

Since β-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane was devoid of analgesic action,[1] the optical forms of the α-diastereoisomer were prepared in order to determine which one of the four stereoisomers of I is responsible for the analgesic activity.

α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol was resolved by fractional crystallization of the *d*-camphorsulfonic acid salt. The optically active carbinol hydrochlorides were prepared from the *d*-camphorsulfonic acid salts. The optically active carbinol hydrochlorides were acylated using propionic anhydride and either triethylamine or pyridine.

Preliminary pharmacological evaluation, using the rat-tail burn technique, has shown the α-*d*-isomer to give the analgesic response. Subcutaneous doses of 10 mg./kg. of the α-*d*-isomer produced an effect equal to that of 20 mg./kg. of the α-*dl*-compound. The α-*l*-isomer gave no response with subcutaneous doses from 10 to 80 mg./kg.

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Experimental[3]

Resolution of α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol.—A solution of 56.7 g. (0.20 mole) of α-*dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol and 46.5 g. (0.20 mole) of *d*-camphorsulfonic acid in 300 ml. of boiling absolute ethanol was prepared and allowed to stand overnight at 0°. A white crystalline solid was collected, dried *in vacuo* and melted at 171–174°, weight 55.5 g. This product after three recrystallizations from ethanol containing 30% acetone melted at 180–181°, weight 34.3 g. (66.4%), $[\alpha]^{25}D$ +64.2° (*c* 0.9 in chloroform). After an additional recrystallization, the α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol *d*-camphorsulfonate melted at 180–181°, weight 31.0 g., $[\alpha]^{25}D$ +64.6° (*c* 1.0 in chloroform).

Anal. Calcd. for $C_{29}H_{41}NO_5S$: C, 67.54; H, 8.01. Found: C, 67.58; H, 7.81.

The original filtrate was concentrated to one-half its volume and diluted with 200 ml. of hot acetone. Upon cooling, a white crystalline material was obtained melting at 172–173°, weight 29.5 g. This product after three recrystallizations from acetone melted at 174–175°, weight 21.2 g. (42.0%) $[\alpha]^{25}D$ −15.2° (*c* 1.0 in chloroform). After an additional recrystallization from acetone the α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol *d*-camphorsulfonate melted at 174–175°, weight 16.0 g., $[\alpha]^{25}D$ −14.3° (*c* 1.0 in chloroform).

Anal. Calcd. for $C_{29}H_{41}NO_5S$: C, 67.54; H, 8.01. Found: C, 67.79; H, 8.03.

α-*d*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—A solution of 26.5 g. (0.051 mole) of α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol *d*-camphorsulfonate in 100 ml. of water was made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether and dried over anhydrous magnesium sulfate. The ether solution then was saturated with anhydrous hydrogen chloride to yield the α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, m.p. 246–247°, weight 16.2 g., $[\alpha]^{25}D$ +54.9° (*c* 0.7 in water).

Anal. Calcd. for $C_{19}H_{25}NO{\cdot}HCl$: C, 71.34; H, 8.19; N, 4.38; Cl, 11.09. Found: C, 71.07; H, 8.35; N, 4.35; Cl, 11.29.

α-1-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—A solution of 14.5 g. (0.028 mole) of α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol *d*-camphorsulfonate in 50 ml. of water was made alkaline with concentrated ammonium hydroxide. The liberated oil was converted to the hydrochloride salt using the same procedure as employed with the α-*d*-isomer. The α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride after three recrystallizations from methanol–ethyl acetate melted at 246–247°, weight 7.4 g., $[\alpha]^{25}D$ −54.7° (*c* 0.7 in water).

Anal. Calcd. for $C_{19}H_{25}NO{\cdot}HCl$: C, 71.34; H, 8.19; N, 4.38, Cl, 11.09. Found: C, 71.06; H, 8.31; N, 4.16; Cl, 11.33.

α-*d*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane Hydrochloride.—A solution of 5.0 g. (0.017 mole) of α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hy-

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(1) A. Pohland and H. R. Sullivan, THIS JOURNAL, **75**, 4458 (1953).

(2) C. M. Gruber, *J. Lab. Clin. Med.*, **44**, 805 (1954).

(3) All melting points are uncorrected.

drochloride, 10.0 ml. of propionic anhydride and 2.0 ml. of triethylamine was heated at 85–90° for 16 hours. The reaction solution was concentrated *in vacuo* and the residue was dissolved in 50 ml. of water. After washing with ether, the aqueous solution was made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether, washed with three 25-ml. portions of cold water, and then dried over anhydrous magnesium sulfate. The ether was distilled and the α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane recrystallized two times from petroleum ether; m.p. 75–76°, weight 3.6 g., $[\alpha]^{25}D$ +67.3° (*c* 0.6 in chloroform).

Anal. Calcd. for $C_{22}H_{29}NO$: C, 77.83; H, 8.62. Found: C, 77.71; H, 8.61.

The hydrochloride salt was prepared in ether using anhydrous hydrogen chloride. The α-*d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride after three recrystallizations from methanol–ethyl acetate melted at 163–164°, $[\alpha]^{25}D$ +59.8° (c 0.6 in water).

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot HCl$: C, 70.28; H, 8.04. Found: C, 70.47; H, 8.07.

α-*l*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane Hydrochloride.—A solution of 3.0 g. (0.0094 mole) of α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, 4.0 ml. of pyridine and 8.0 ml. of propionic anhydride was refluxed for five hours. The excess propionic anhydride, propionic acid and pyridine were removed *in vacuo* and the residue dissolved in water. After washing once with ether, the aqueous solution was made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether and dried over anhydrous magnesium sulfate. The ether was distilled and the α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane recrystallized two times from petroleum ether; m.p. 75–76°, weight 1.9 g., $[\alpha]^{25}D$ −68.2° (*c* 0.6 in chloroform).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.83; H, 8.62. Found: C, 77.65; H, 8.62.

The hydrochloride salt was prepared in ether solution using anhydrous hydrogen chloride. The α-*l*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride after three recrystallizations from methanol–ethyl acetate melted at 163–164°, $[\alpha]^{25}D$ −60.1° (*c* 0.7 in water).

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot HCl$: C, 70.28; H, 8.04. Found: C, 70.28; H, 8.07.

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Arylation of Unsaturated Systems by Free Radicals. IV.[1] Effects of Catalyst, *p*H and Solvent upon the Meerwein Reaction

BY CHRISTIAN S. RONDESTVEDT, JR., AND O. VOGL[2]

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The Meerwein reaction involves arylation of a conjugated unsaturated system by a diazonium salt in a buffered aqueous acetone solution at *p*H 3 in the presence of cupric chloride.[3] The effect of the structure of the diazonium salt has been investigated by several workers[3] and the effect of the nature of the unsaturated constituent is now under investigation. However, no systematic study of the numerous other variables has been recorded.

In this work we report the effects of varying the metal catalyst, the solvent, the *p*H and the buffer ingredients. The reaction of *p*-nitrobenzenediazonium chloride and coumarin was selected for study since good yields can be obtained using the "standard" conditions outlined by Meerwein,[4] and the product is easily isolated. A standardized procedure was adopted and the variables were changed one at a time. The results are presented in Tables I–IV.

Cupric chloride is by far the most effective catalyst. Slight catalytic activity was noted with zinc, cadmium and mercuric salts, as well as with copper powder, when compared to the results in blank runs with no added catalysts. The remarkable activity of cupric salts appears to be derived from the "irregularity" in the electronic configuration of copper. It should be noted that small yields are obtained even in the absence of catalyst. This may be a measure of the simple radical process suggested by Koelsch[5] and Müller.[6]

Acetone was the best solvent, followed by acetonitrile. Unsaturation in the solvent exerts a beneficial effect upon the Meerwein reaction, indicating that the solvent is involved in some fundamental way in the intermediate complex.[1,3]

Table III emphasizes the *p*H dependence; the best results in an acetate buffer were obtained at *p*H 2–4. At low *p*H, competition with the Sandmeyer reaction becomes important, while at *p*H 5 the resinous character of the crude product points out the other modes of decomposition available to the diazonium salt.

It was surprising to note the dependence on buffer composition at constant *p*H 3. Acetate is the best; Meerwein's report[4] indicates that chloroacetate is similar in behavior. Perhaps the succinate results derive from an entropy difference in forming the intermediate complex with the large acid; alternatively, since acetic acid is weaker than succinic, the difference may reflect merely the fraction dissociated. Addition of cupric complexing agents, as expected, reduces the catalyst efficiency markedly, the effect being least with citrate and greatest with ethylenediaminetetraacetic acid (Versene).

Experimental

Catalyst Experiments.—*p*-Nitroaniline (0.03 mole) was diazotized with 25 ml. of 1:1 hydrochloric acid, 15 g. of ice and 7.0 ml. of 30% sodium nitrite solution. Sodium acetate was added to give *p*H 4 (*p*H paper), followed by 75–90 ml. of acetone and 0.03 mole of coumarin. Finally 0.0045 mole of the catalyst was added to the solution maintained at 0–5°. After stirring until nitrogen evolution was complete, the mixture was steam distilled. The water-insoluble residue in the flask was collected by filtration, washed with water and acetone (3-*p*-nitrophenylcoumarin is almost insoluble in acetone), and recrystallized from anisole (10–12 ml. per gram). The crude melting points are given in Table I as an indication of purity; once-recrystallized material generally melted at 262–264°.

When the reaction mixture was worked up by evaporating the acetone without heating, the yields were lower. Perhaps an intermediate chloro compound is formed to some extent, and it is lost during the acetone washing, whereas steam distillation converts it to 3-*p*-nitrophenylcoumarin.

Solvent Dependence.—*p*-Nitroaniline (0.03 mole) was diazotized as before. The *p*H was adjusted to 3.5 (short-range *p*H paper) with sodium acetate, and 0.0045 mole of $CuCl_2$ was added. This solution was then added to 0.03 mole of coumarin in 90 ml. of the solvent at 0–5°. After

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[1] Paper III, O. Vogl and C. S. Rondestvedt, Jr., THIS JOURNAL, **77**, 3067 (1955).

[2] On leave from University of Vienna, Austria.

[3] For a literature survey, see C. S. Rondestvedt, Jr., and O. Vogl, *ibid*, **77**, 2313 (1955).

[4] H. Meerwein, E. Buchner and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

[5] C. F. Koelsch and V. Boekelheide, THIS JOURNAL, **66**, 412 (1944).

[6] E. Müller, *Angew. Chem.*, **61**, 179 (1949).