[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

# OPTICALLY ACTIVE HYPNOTICS

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It is a well known fact that the physiological properties of many optical isomers are quite different even though their physical properties are the same in every respect except for their action on plane polarized light. The best known theory to explain the action of hypnotics is that of Overton and Meyer,[1] who have shown the close association of the physiological activity of hypnotics with their distribution coefficient for water and fat solutions. If optically active hypnotics were tested pharmacologically, some evidence in favor of or against this theory should result. If hypnotic action is largely due to the physical properties of the drug, then the dextro and laevo isomers of any hypnotic compound should have the same physiological action, which might or might not be different from that of the racemic substance. On the other hand, if the physiological properties are largely dependent on the molecular structure of the compound, the two active isomers would be expected to have different hypnotic actions and the racemic substance would fall between in its behavior.

The commonest hypnotics in practical use are the derivatives of barbituric acid. The simplest known derivative of this group with a fair degree of hypnotic action and an asymmetric alkyl group is ethyl-*sec.*-butylbarbituric acid. This substance was prepared by the method of Shonle and Moment.[2] The compound which was obtained melted at 197° instead of 155–157° as given by them. Its purity was demonstrated by analyses. No convenient method of resolution was found as the barbituric acid derivative did not seem to be a strong enough acid to form stable salts with the alkaloids or other optically active amines which were available.

Another possible method of obtaining an optically active barbituric acid is to prepare an active alcohol, convert it successively to the bromide, then to the alkylmalonic ester derivative and finally to the barbituric acid derivative. Since secondary octyl alcohol (octanol-2) is readily available and quite easily resolved by Kenyon's[3] procedure, it was decided to use it as a starting point. It was thought that ethyl-*sec.*-octylbarbituric acid should have a sufficiently strong physiological action for the purpose of determining the difference in the action of the optical iso-

[1] Overton, "Studien über die Narkose, zugleich ein Betrag zur Allgemeinen Physiologie," Jena, G. Fischer, **1901**, p. 70; Meyer, *Arch. exp. Path. Pharmakol.*, **42**, 109, 119 (1901).

[2] Shonle and Moment, THIS JOURNAL, **45**, 243 (1923).

[3] Kenyon, *J. Chem. Soc.*, **121**, 2540 (1922); "Organic Syntheses," John Wiley and Sons, Inc., New York, **1926**, Vol. VI, p. 68.

mers. Accordingly the three optical isomers of this substance were prepared.

The active *sec.*-octyl alcohols used for the syntheses had the rotations of ± 9.9°. The bromide of the inactive form was made first and it was found that slightly better yields could be obtained from the alcohol and phosphorus tribromide than from the alcohol and hydrobromic acid either with or without the addition of sulfuric acid. Accordingly the active bromides were made from the active alcohols by this same procedure. The bromides thus obtained had rotations of +34.05° and −34.25°, which are higher than reported for the same bromides made by the hydrobromic acid method. Levene and Mikeska[4] report a rotation of +14.56° for the dextro isomer and Pickard and Kenyon[5] report rotations of ±27.5 for the bromides.

The bromides were allowed to react with an excess of the sodium derivative of diethyl ethylmalonate in order to obtain the best possible yields of diethyl ethyl-*sec.*-octylmalonate. The rotations of the active esters were +8.22° and −8.07°. There was no change in the sign of rotation in going from the bromide to the malonic ester derivative.

The barbituric acid derivatives were prepared by the usual procedure of condensing the malonic ester derivative with urea in the presence of sodium ethylate. The inactive derivative melted at 126–127°, whereas the active isomers melted at 107°. The rotations of the active forms were +7° and −7.02°. It is not certain that some racemization did not occur in these different steps. However, the close agreement between the rotations of the dextro and the laevo forms showed that they were of the same degree of purity and that valid conclusions could be drawn from pharmacological tests made with these substances.

The pharmacological tests were carried out by Mr. H. C. Spruth at the Abbott Laboratories.[6] The minimum effective dose (M. E. D.) and the minimum fatal dose (M. F. D.) were determined on albino rats according to the method of Nielsen, Higgins and Spruth.[7] These data are recorded in Table I.

The errors in data of this kind are sometimes as much as 10%. However, since the determinations were made by one worker they may be safely used for comparison.

These results show that there is practically no difference in the physiological activity (either hypnotic action or toxicity) of the dextro and laevo isomers. This tends to confirm the view that physical properties are the most important factors in determining the activity of an hypnotic of this

[4] Levene and Mikeska, *J. Biol. Chem.*, **59**, 475 (1924).

[5] Pickard and Kenyon, *Ber.*, **45**, 1593 (1912).

[6] The authors desire to express their thanks to Mr. Carl Nielsen and Mr. Henry C. Spruth of the Abbott Laboratories for their assistance in this investigation.

[7] Nielsen, Higgins and Spruth, *J. Pharmacol.*, **26**, 371 (1925).

series. There seems to be no difference between the effect of the active form and of the racemic form.

TABLE I

PHARMACOLOGICAL DATA ON THE *d*-, *l*- AND *dl*-5-ETHYL-5-*sec.*-OCTYLBARBITURIC ACIDS

| | M. F. D. in mg. per g. of rat | Ratio of toxicity, barbital = 1 | M. E. D. in mg. per g. of rat | Ratio of efficiency, barbital = 1 | Safety margin, % |
|---|---|---|---|---|---|
| *dl*-isomer | 1.90[a] | 0.16 | 0.37 | 0.61 | 80.5[c] |
| *d*-isomer | 1.85 | .17 | .38 | .59 | 79 |
| *l*-isomer | [b] | .. | .36 | .62 | .. |

[a] The toxicity figures were determined with 10% solutions of the sodium salts.

[b] A definite M. F. D. could not be determined for this isomer because of the small supply of material available and certain inconsistencies in the results, but from the work done it may be said that the toxicity is approximately the same as that of the other two compounds.

[c] The safety margin is the difference between the M. F. D. and the M. E. D. expressed in percentage of the M. F. D.

## Experimental Part

***dl*-2-Bromo-octane.**—Three different procedures were employed in this preparation, one using the alcohol with sulfuric acid and hydrobromic acid, one using only hydrobromic acid and the alcohol, and the last using phosphorus tribromide with the alcohol.

**Hydrobromic Acid-Sulfuric Acid Method.**—One mole (130 g.) of crude capryl alcohol (b. p. 165–170°), 2 moles (340 g.) of 48% hydrobromic acid solution and 0.25 mole (25 g.) of concd. sulfuric acid were refluxed for about five hours and then steam distilled. The bromide layer was separated from the water, washed successively with ice-cold concd. sulfuric acid, water, sodium carbonate solution and finally with water, and dried over calcium chloride. A yield of 95 g. (49% of the theoretical amount), b. p. 71–73° at 14 mm., was obtained on distilling the product.

**Hydrobromic Acid Method.**—The same quantities of alcohol and hydrobromic acid without the sulfuric acid were used and the mixture was refluxed as before. The bromide-alcohol mixture was distilled, separated from the water layer and again treated with two moles of hydrobromic acid solution. The final yield of purified product was 10% lower than when a little sulfuric acid was used.

**Phosphorus Tribromide Method.**—In a 2-liter, three-necked flask, fitted with a mechanical stirrer, a thermometer reaching nearly to the bottom of the flask and a separatory funnel, was placed 130 g. of crude capryl alcohol (b. p. 165–170°). The stirrer was started and after cooling the alcohol to −5°, 298 g. of phosphorus tribromide was added drop by drop at such a rate that the temperature did not go above +5°. This required about two hours. The mixture was allowed to stand overnight and thus gradually come to room temperature. The thermometer was removed and a tube to carry off fumes of hydrogen bromide was put in its place. The mixture was heated on a steam-bath for one hour. Then to it was added first, slowly, about 300 cc. of cold water and then about 150 cc. of ether to aid in the separation of the bromide. The ether solution was separated, washed with sodium carbonate solution and water, dried over calcium chloride and distilled. The yield of bromide, b. p. 71–73° at 14 mm., was 98 g. (51% of the theoretical amount). The low yields by all of the methods can undoubtedly be traced in part to the fact that the capryl alcohol was prepared by the distillation of a mixture of castor oil and sodium hydroxide and was purified only by fractional distillation.

The bromide boils at 61° at 3 mm., 66° at 6 mm., 72° at 14 mm.; $d_4^{25}$ = 1.0878; $n_D^{25}$ = 1.4442, $M_D$, calcd., 46.92; obs. 47.00.

*l*-2-Bromo-octane.—The procedure used in this preparation is the same as described for the inactive bromide by the phosphorus tribromide method. From 76 g. of *d*-octanol-2 ($[\alpha]_D^{25} = +9.9°$) and 174 g. of phosphorus tribromide, there was obtained 91 g. (80% of the theoretical amount) of *l*-2-bromo-octane, b. p. 60° at 3 mm., 71° at 14 mm.; $d_4^{25} = 1.0982$; $n_D^{25} = 1.4475$; $M_D$, calcd., 46.92; obs., 46.87; $[\alpha]_D^{25} = -34.25°$.

*Anal.* (Stepanoff). Subs. 0.1964 g.: 10.1 cc. of 0.1000 *N* $AgNO_3$. Calcd. for $C_8H_{17}Br$: Br, 41.17. Found: 41.18.

*d*-2-Bromo-octane.—From 55 g. of *l*-octanol-2 ($[\alpha]_D^{25} = -9.9°$) and 126 g. of phosphorus tribromide, there was obtained 66 g. (80% of the theoretical amount) of *d*-2-bromo-octane. The physical constants were identical with those of the laevo isomer except for the rotation, $[\alpha]_D^{25} = +34.2°$.

*dl*-Diethyl Ethyl-*sec.*-octylmalonate.—The common procedure for the preparation of a substituted malonic ester was followed.[8] It was found by experiment that the best yields were obtained when a rather large excess of the sodium derivative of diethyl ethylmalonate was used. The amounts of reagents used were as follows: 150 cc. of absolute alcohol, 8.65 g. of sodium, 94 g. of diethyl ethylmalonate and 48 g. of *dl*-2-bromo-octane. The yield of ester was 32.5 g. (43% of the theoretical amount), b. p. 135–140° at 3 mm., 137–142° at 6 mm., 158–165° at 17 mm., 170–175° at 27 mm.; $d_4^{25} = 0.9434$; $n_D^{26} = 1.4365$; $M_D$, calcd., 84.04; obs., 83.75.

*Anal.* Subs., 0.1904: $CO_2$, 0.4740; $H_2O$, 0.1825. Calcd. for $C_{17}H_{32}O_4$; C, 68.00; H, 10.67. Found: C, 67.80; H, 10.64.

*d*-Diethyl Ethyl-*sec.*-octylmalonate.—By the same procedure, from 230 cc. of absolute alcohol, 11.8 g. of sodium, 129 g. of diethyl ethylmalonate and 66 g. of *d*-2-bromo-octane, there was obtained 42 g. (41% of the theoretical amount) of *d*-ester, b. p. 137–138° at 3 mm.; $d_4^{25} = 0.9323$; $n_D^{25} = 1.4370$; $M_D$, calcd., 84.04; obs., 83.95; $[\alpha]_D^{25} = +8.22°$.

*Anal.* Subs., 0.2000: $CO_2$, 0.4971; $H_2O$, 0.1925. Calcd. for $C_{17}H_{32}O_4$; C, 68.00; H, 10.67. Found: C, 67.91; H, 10.69.

*l*-Diethyl Ethyl-*sec.*-octylmalonate.—From 300 cc. of absolute alcohol, 16.3 g. of sodium, 177 g. of diethyl ethylmalonate and 91 g. of *l*-2-bromo-octane, there was obtained 59 g. (41% of the theoretical amount) of the *l*-ester; $[\alpha]_D^{25} = -8.07°$. The other physical constants were identical with those of the dextro isomer.

*dl*-5-Ethyl-5-*sec.*-octylbarbituric Acid.—A solution of 23.25 g. of diethyl ethyl-*sec.*-octylmalonate, 5.37 g. of sodium and 6.7 g. of dry urea in 150 cc. of absolute alcohol (dried with magnesium methylate) was refluxed in an oil-bath held at 105–110° for one hour. The condenser was then set for distillation and the alcohol was removed by distillation. This required about three hours. The reaction mixture was held at the temperature of 105–110° for about an hour after the alcohol was removed. The contents of the flask were then dissolved in about 200 cc. of water and the solution was acidified with concd. hydrochloric acid. The barbituric acid derivative separated as an oil which solidified when the mixture was allowed to stand overnight or when it was cooled in an ice-bath. This crude product was filtered, crushed in a mortar and washed thoroughly with water. It was then recrystallized from about 300 cc. of 60% acetic acid from which it separated in long needles. The yield was 10 g. (48% of the theoretical amount) of a product, m. p. 126–127°.

*Anal.* (Kjeldahl). Subs. 0.2000: 14.6 cc. of 0.1000 *N* HCl. Calcd. for $C_{14}H_{24}O_3N_2$: N. 10.47. Found: 10.22.

[8] Adams and Kamm, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1925, Vol. IV, p. 11.

**d-5-Ethyl-5-*sec.*-octylbarbituric Acid.**—The procedure was identical with that described above. However, the yield was only 26.5% of the theoretical amount. The product melted at 107°; $[\alpha]_D^{25} = +7°$ (2 g. in 15 cc. of alcohol).

*Anal.* Subs. 0.2000: 14.8 cc. of 0.1000 *N* HCl. Calcd. for $C_{14}H_{24}O_3N_2$: N, 10.47. Found: 10.36.

**l-5-Ethyl-5-*sec.*-octylbarbituric Acid.**—This was prepared in exactly the same manner and the yield was identical with that of the dextro compound, $[\alpha]_D^{25} = -7.02°$ (2 g. in 15 cc. of alcohol). In other respects it was identical with the dextro isomer.

## Summary

1. The *d*-, *l*- and *dl*-isomers of 5-ethyl-5-*sec.*-octylbarbituric acid have been prepared.

2. Pharmacological tests show that there is almost no difference in physiological action between the *d*- and *l*-isomers.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# CATALYSIS WITH COPPER IN THE ULLMANN REACTION

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Professor Fritz Ullmann[1] discovered that the addition of copper catalyzed the reaction of aryl halides with aryl amines or N-acyl aryl amines to form N-aryl aryl amines and of salts of phenols with aryl halides to form di-aryl ethers. A high boiling solvent (nitrobenzene or phenol) was used and potassium carbonate added to neutralize the halogen acid formed.

In most of the later work a special copper was used as a catalyst. This "Naturkupfer C," is a finely divided product obtained by grinding metallic copper under oil between mill stones. However, in some cases other forms of copper and even copper compounds gave equally good results. There has been little information available to indicate whether the reaction involved a case of heterogeneous or homogeneous catalysis, as to what was the real catalyst and why there was such a variation in the results obtained in using different reactants and different samples of copper or copper compounds.

A rather intensive study has been made of the reaction of phenyl bromide

[1] (a) Ullmann, *Ber.*, **36**, 2382 (1903); (b) Ullmann and Sponagel, *Ber.*, **38**, 2211 (1905); (c) Irma Goldberg, *Ber.*, **39**, 1691 (1906); (d) *Ber.*, **40**, 4541 (1907); (e) Ullmann, *Ann.*, **355**, 312 (1907); (f) British patents: 2949 (1912), *C. A.*, **7**, 2477 (1913); 16,272 (1910), *C. A.*, **5**, 3121 (1911); 16,440 (1910), *C. A.*, **5**, 3165 (1911); (g) French patent: 418,210 (1910), *C. A.*, **6**, (1912); (h) German patents: 173,523 (1905), *C. A.*, **1**, 513 (1907); 185,663 (1906), *C. A.*, **2**, 351 (1908); 187,870 (1906), *C. A.*, **2**, 602 (1908); 224,982 (1909), *C. A.*, **5**, 213 (1911); 238,106 (1910), *C. A.*, **6**, 1680 (1912); 248,999 (1910), *C. A.*, **6**, 2851 (1912).