TABLE I

POLARIZATION AND DENSITIES OF BENZENE-ETHYLENE DICHLORIDE MIXTURES

Mole frac. $C_2H_4Cl_2$	Dielectric constant	$P_{1,2}$	P_2	d^{25}_4 obs.	d^{25} calcd.	Deviation
0.000				0.8739		
.113	2.791	33.096	83.698	.9086	0.9085	−0.0001
.211	3.318	38.077	80.805	.9397	.9400	+ .0003
.342	3.879	41.980	71.468	.9863	.9844	− .0019
.446	4.707	46.912	72.081	1.0192	1.0214	+ .0022
.605	5.914	51.406	67.568	1.0802	1.0810	+ .0008
.719	6.940	54.137	64.878	1.1247	1.1261	+ .0014
.857	8.455	56.734	61.753	1.1846	1.1832	− .0014
1.000	10.365	58.959	58.959	1.2453		

ethylene dichloride calculated from the measured densities. Figure 1 is a plot of P_2 *versus* mole fraction including the values of Gross.[3]

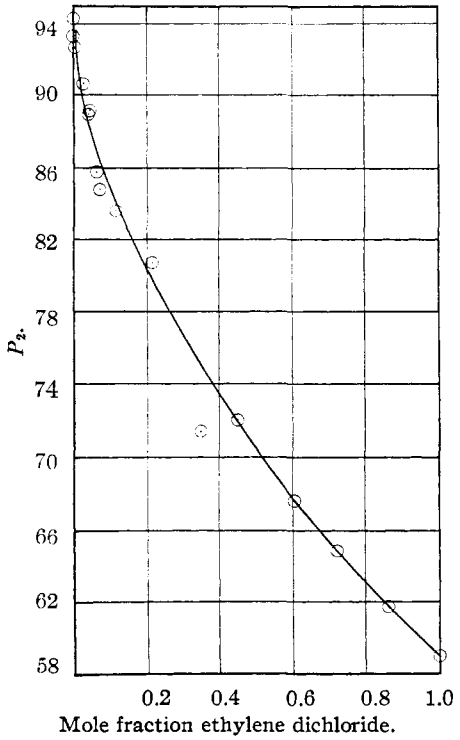


Fig. 1.—Polarization of ethylene dichloride in benzene solutions.

NORTHEASTERN UNIVERSITY
BOSTON, MASS.

RECEIVED JULY 2, 1948

The Preparation of 6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline

BY JOHN WEIJLARD, EDWARD F. SWANEZY AND ELEANOR TASHJIAN

Perparin, 6,7-diethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline, the tetraethyl analog of papaverine, is reported to be more active than papaverine as an antispasmodic.[1] Although its preparation from N-(3,4-diethoxyphenylacetyl)-β-hydroxy-β-(3,4-diethoxyphenyl)-ethylamine has been reported,[2] the details are meager, and the preparation and characterization of the requisite intermediates are not recorded.

We have prepared perparin from N-(3,4-diethoxyphenylacetyl)-β-(3,4-diethoxyphenyl)-ethylamine by ring closure to the dihydroisoquinoline, and dehydrogenation of the latter, the same series of steps that were employed by Kindler and Peschke for the preparation of papaverine.[3]

β-(3,4-Diethoxyphenyl)-ethylamine, required for the preparation of the amide, was prepared by catalytic hydrogenation of 3,4-diethoxymandelonitrile.

Experimental

3,4-Diethoxybenzaldehyde.[4]—Six hundred and sixty-four grams of ethyl vanillin (4 moles) was mixed with 400 cc. of diethyl sulfate (472 g., 3 moles), the pasty mixture was stirred in a stainless steel container while 680 cc. of 30% sodium hydroxide solution was added in 30–40-cc. portions over a period of one hour. The temperature was about 40°. The mixture was warmed to 80° when complete solution was obtained. The solution was held at 80–82° and rapidly stirred while 440 cc. of additional diethyl sulfate (520 g., 3.4 moles) was added in 20–30-cc. portions over a period of one hour. The solution was stirred for another half-hour at 80°, then 120 cc. of 30% sodium hydroxide was added and stirred an additional ten minutes. The solution was cooled to room temperature and extracted with ether, the ether extract was washed with 5% sodium hydroxide solution, then with water until free from alkali. The ether was distilled and the residue was dried *in vacuo;* yield 736 g. (95%) of a nearly water white sirup which was used without further purification in the experiments. A sample for analysis was distilled and practically all distilled at 128–130° and 2 mm. pressure.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.26. Found: C, 67.83; H, 7.46.

3,4-Diethoxymandelonitrile.—This compound was made from 3,4-diethoxybenzaldehyde in nearly quantitative yields according to directions for 3,4-dimethoxymandelonitrile.[5] The melting point is 42–43°.[6]

β-(3,4-Diethoxyphenyl)-ethylamine.[7]—Sixty-six grams of the crude 3,4-diethoxymandelonitrile (0.3 mole) was dissolved in 400 cc. of alcohol, 30 cc. of concd. aqueous hydrochloric acid was added followed by 1.5 g. of platinum oxide, then hydrogenated at 10 to 20 lb. of pressure. About 75% of the theoretically required hydrogen was absorbed in six hours, then the reduction stopped. The catalyst was filtered and the solution concentrated to dryness *in vacuo*. The residue was dissolved in water and extracted with ether to remove substances that had not been reduced. To the solution was added 75 cc. of 30% sodium hydroxide, the precipitated amine was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The ether was removed *in vacuo*, and the residue distilled at about 125° and 1 mm. pressure; yield 26.6 g. (42.4%).

(1) Issekutz, Leinzinger and Dirner, *Arch. exp. Path. Pharmakol.*, **164**, 158 (1932).

(2) Wolf, U. S. Patent 1,962,224; *C. A.*, **28**, 4841 (1934).

(3) Kindler and Peschke, *Arch. d. Pharm.*, **272**, 236–241 (1934).

(4) Prepared by Ide and Buck, THIS JOURNAL, **54**, 3305 (1932), but since no experimental details were given, the preparation is included here.

(5) Pictet and Gams, *Ber.*, **42**, 2949 (1909).

(6) Incidentally, the compound was found to be a convenient starting material for the preparation of 3,4-diethoxymandelic acid ester by cold esterification of the nitrile in alcohol with hydrochloric acid, and for the preparation of 3,4-diethoxymandelic acid by mild hydrolysis of the ester.

(7) Prepared previously by electrolytic reduction of 3,4-diethoxy-ω-nitrostyrene by Slotta and Haberland, *Angew. Chem.*, **46**, 769 (1933).

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.93; H, 9.18; N, 6.33.

N-(3,4-Diethoxyphenylacetyl)-β-(3,4-diethoxyphenyl)-ethylamine.—A mixture of 10.45 g. of β-(3,4-diethoxyphenyl)-ethylamine (0.05 mole) and 11.65 g. of technical grade 3,4-diethoxyphenylacetic acid[8] (0.052 mole) was held at 180–195° for one hour. The water formed was swept out with a current of nitrogen. The reaction mixture was dissolved in 50 cc. of hot toluene and chilled at 2°. The crystals were collected and washed with petroleum ether; yield 16.5 g. (79.5%), m. p. 102–103°.

Anal. Calcd. for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.43; H, 8.27; N, 3.46.

6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-3,4-dihydroisoquinoline.—Forty-eight grams of N-(3,4-diethoxyphenylacetyl)-β-(3,4-diethoxyphenyl)-ethylamine (0.115 mole) was suspended in 200 cc. of benzene; the air was replaced with carbon dioxide, then 23 cc. of phosphorus oxychloride (about 0.25 mole) was added, and the mixture was stirred mechanically and refluxed in a carbon dioxide atmosphere for one hundred minutes. The benzene and excess phosphorus oxychloride was distilled *in vacuo*, and the residual sirup was dissolved in 150 cc. of benzene and poured on cracked ice. Then an excess of concd. ammonia was added and the mixture agitated thoroughly. The ammoniacal layer was separated and again extracted with 100 cc. of benzene. The combined benzene extracts were washed with 2–150-cc. portions of 5% ammonia water, then water, and dried over anhydrous sodium sulfate. The benzene was distilled *in vacuo*, the residue was agitated with 400 cc. of petroleum ether and chilled at 2° overnight. The crystals were filtered and washed with petroleum ether; yield 44.5 g. (97%), m. p. 74–75°.

6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline.—Forty-two grams of crude 6,7-diethoxy-1-(3′,4′-diethoxybenzyl)-3,4-dihydroisoquinoline (0.1056 mole) was dissolved in 168 cc. of diisopropylbenzene, 2 g. of 5% palladium-on-charcoal was added, the air was replaced with carbon dioxide, and the mixture refluxed for two hours. The catalyst was filtered, the filtrate was cooled to 30° and mixed with 350 cc. of petroleum ether, then chilled at 2° overnight. The crystals were washed with petroleum ether; yield 37.5 g. (90%), m. p. 95–96°. After suitable purification the base melted at 99–100°.

Anal. Calcd. for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39; N, 3.54. Found: C, 73.08; H, 7.81; N, 3.79.

The hydrochloride, prepared by adding alcoholic hydrochloric acid to an alcoholic solution of the base, melted at 186–188°.

Anal. Calcd. for $C_{24}H_{30}O_4NCl$: C, 66.72; H, 7.00; N, 3.24. Found: C, 66.69; H, 7.12; N, 3.42.

(8) Kindler and Gehlhaar, *Arch. d. Pharm.*, **274**, 377 (1936).

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, N. J.

RECEIVED OCTOBER 22, 1948

A Michael Reaction of Lawsone

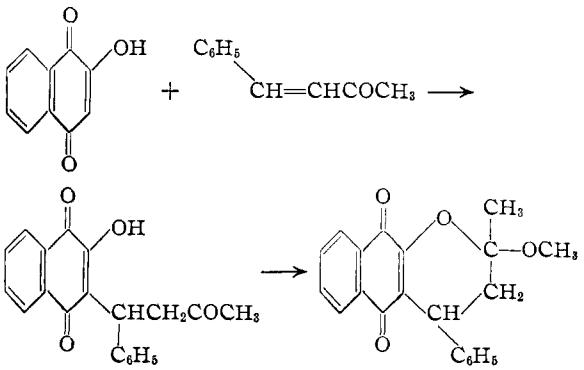
BY HAROLD E. ZAUGG

In connection with the preparation of various 3-substituted-2-hydroxy-1,4-naphthoquinones for application to antimalarial studies,[1] the present author found that lawsone (2-hydroxy-1,4-naphthoquinone) would react with benzalacetone in pyridine to give an addition product resulting from a Michael type reaction. In this respect, lawsone is similar in reactivity to 4-hydroxycoumarin which likewise has been found[2] to add to various α,β-unsaturated ketones.

(1) Fieser, Leffler, *et al.*, THIS JOURNAL, **70**, 3151 (1948).

(2) Ikawa, Stahmann and Link, *ibid.*, **66**, 902 (1944).

The structure of the product was demonstrated by analysis and by ring-closure to a cyclic ketal.[2] The two reactions are summarized as



Since both the quinone adduct and its cyclization product were found[3] to be entirely inactive against *P. lophurae* in ducks, no extension of this reaction to other α,β-unsaturated ketones was attempted.

Experimental

The Michael Condensation.—A solution of 34.8 g. (0.2 mole) of lawsone and 29.2 g. (0.2 mole) of benzalacetone in 150 cc. of pyridine was refluxed for five hours and poured into ice-water containing 200 cc. of concentrated hydrochloric acid. The tarry precipitate was then taken up in ether, washed with dilute hydrochloric acid and filtered from insoluble material. The ether solution was extracted with two 400-cc. portions of saturated sodium bicarbonate solution. These deep red solutions were combined to form fraction I. Six more extractions with 300-cc. portions of saturated bicarbonate were combined to form fraction II. The ether layer was concentrated to dryness and the residue dissolved in 250 cc. of 5% sodium hydroxide solution and filtered from insoluble material to form fraction III.

Fraction I was acidified with hydrochloric acid to give 7.0 g. of yellow precipitate of m. p. 130–160° apparently containing a considerable proportion of starting material. This solid was warmed gently with 300 cc. of a 10% sodium bisulfite solution and any insoluble material was filtered off and dissolved in ether. The ether solution was washed successively with 10% sodium acetate, dilute hydrochloric acid and water, and dried over anhydrous magnesium sulfate. Filtration and concentration of the ether to a volume of about 40 cc. followed by cooling in ice and filtering gave 1.7 g. of light yellow powder, m. p. 143–144°.

Fraction II was acidified with concentrated hydrochloric acid, the brown precipitate was filtered off and triturated with a large excess of saturated sodium bicarbonate solution until no more solid appeared to dissolve. The solution was filtered through a thin layer of Norite and acidified again with hydrochloric acid. The precipitate was taken up in a relatively large volume of ether, washed with water and dried over anhydrous magnesium sulfate. Filtration and treatment of the ether solution in the same way as that of fraction I gave 2.3 g. of light yellow powder, m. p. 142–144°.

Fraction III was stirred with 50–75 g. of Nuchar at room temperature and filtered through a layer of Nuchar. The filtrate was discarded and the filter cake was stirred at room temperature with 300 cc. of 5% sodium hydroxide, filtered and washed with 700 cc. of water. The filtrate was acidified and the brown precipitate formed was treated in exactly the same manner as was the brown product

(3) Antimalarial tests were carried out by Drs. A. P. Richardson and R. Hewitt at the University of Tennessee, Department of Pharmacology.