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1,2-DIPHENYL-2-AMINOETHANOLS. I. SYNTHESIS OF SOME *erythro*-1,2-DIPHENYL-2-ALKYLAMINOETHANOLS

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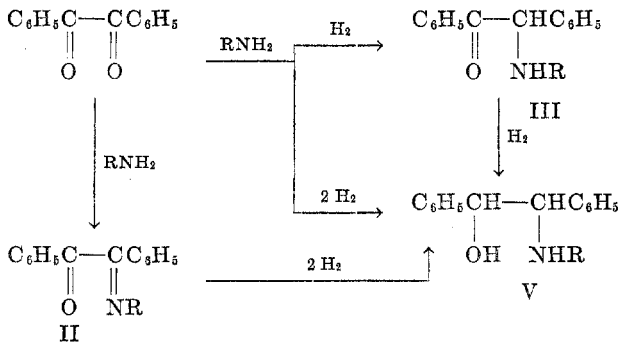
The announcement that 1,2-diphenyl-2-aminoethanol (I) could replace

$$C_6H_5CH(OH)CH(NH_2)C_6H_5$$
I

morphine as an analgesic (1) evoked considerable interest in this type of compound. Unfortunately, early communications failed to identify the particular stereoisomer used (1, 2) and since I contains two asymmetric carbon atoms, four isomers are theoretically possible. The recent elucidation of the exact structure of these two racemic pairs (4) has now allowed correlation of structure with pharmacological activity. The *erythro* racemate is inactive as an analgesic, the *threo* racemate weakly active in mice (3). It is peculiar that although the *threo* racemate is reported to have some analgesic activity, the individual *threo* enantiomorphs are stated to be inactive.[1]

Investigation of the 1,2-diphenyl-2-aminoethanols as potential therapeutic agents led us to prepare a series of these aminoalcohols of both the *erythro* and *threo* configurations, containing substituents on the nitrogen atom. We wish to communicate at this time the preparation of a series of *erythro*-1,2-diphenyl-2-alkylaminoethanols (V), together with some observations concerning the mechanism of the preparative method.



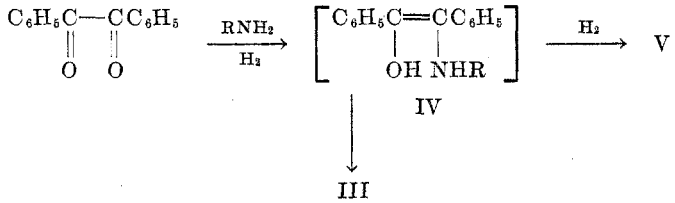
(See Table I for identification of R)

The utility of the reductive amination process suggested that this reaction might be ideal for the preparation of such aminoalcohols (8). Indeed, several isolated examples of the reductive amination of benzil and benzoin with primary amines are in the literature (5, 6, 9). In our hands, the reductive amination of benzil with a primary amine over Raney nickel at low pressure provided a

[1] The terms "*erythro*" and "*threo*" are now used for this type of compound. In the older literature the nomenclature was "diphenylhydroxyethylamine" and "iso-diphenylhydroxyethylamine," respectively (5).

convenient laboratory synthesis for the 1,2-diphenyl-2-alkylaminoethanols. Yields were frequently high and the products could be purified readily, since under optimum conditions by-products occurred in low yield. It is significant that this reaction gives the aminoalcohols having the *erythro* configuration exclusively; no trace of the *threo* isomers could be detected. Benzil can be replaced by benzoin only at the expense of a decrease in yield of basic material and a corresponding increase in yield of neutral material (hydrobenzoin).

The experimental facts are consistent with a mechanism in which benzil and the amine react to form the Schiff's base (II), which is subsequently reduced to the aminoalcohol (V). This reduction may involve an intermediate enol, analagous to the course of hydrogenation of benzils (11). The sterospecificity noted is



then a consequence of a 1,4 addition of hydrogen to the Schiff's base, which would be most likely to occur if the nitrogen and oxygen atoms were close to each other at the time of contact with the catalyst-hydrogen complex. The resulting enol (IV) would of necessity be of the cis configuration, and on further hydrogenation could give only the *erythro* aminoalcohol.

With methylamine, benzil gives consistently higher yields of aminoalcohol than does benzoin; 80–90% from benzil as compared to 55–65% from benzoin. This indicates that benzil reacts directly with the amine and is not first reduced to benzoin, although this reduction does occur under the experimental conditions used. Confirmation of this is found in that benzil and methylamine give II (R = CH_3) in 84% yield in a matter of a few minutes, while benzoin is recovered to the extent of nearly 40% after refluxing for 30 minutes in methanol with methylamine. If a mixture of benzil and excess methylamine is hydrogenated over Raney nickel, the reaction is distinctly two-step, absorption of the first mole of hydrogen being some 15 times as rapid as that of the second mole. Interruption of the hydrogenation at the half-way point allows isolation of III (R = CH_3) in high yield, which can be subsequently hydrogenated to V. The aminoketone may result from a 1,2 addition of hydrogen to the N=C bond, or as suggested above may involve a 1,4 addition, followed by ketonization. If the Schiff's base is isolated and hydrogenated, two moles of hydrogen are absorbed at an essentially constant and rapid rate, and only V can be isolated. Reductive amination over platinum oxide gives V, while over palladium-on-carbon III is obtained (*cf.* 9, 10).

In Table I are summarized the 1,2-diphenyl-2-alkylaminoethanols which were prepared in this work. Previously only Vb and Ve had been prepared by reductive amination; the other known aminoalcohols had been synthesized by different methods. The general procedure was to mix the benzil and amine together in methanol, add the catalyst, and start hydrogenation immediately. Following

removal of the catalyst at the end of the reaction, isolation of the aminoalcohol could be accomplished easily by concentrating and chilling the filtrate. In some cases, the filtrate was evaporated to dryness, and the residue was taken up in toluene and stirred with dilute hydrochloric acid. The hydrochloride was then collected.

The above procedure was satisfactory only for primary carbinamines, which react with benzil rapidly enough so that reduction of the benzil is unimportant. With secondary and tertiary carbinamines, it is necessary to allow the benzil and amine sufficient time to form the Schiff's base prior to hydrogenation; otherwise, the main product is hydrobenzoin. In such cases, the Schiff's bases were isolated and then hydrogenated. Benzil may be reductively aminated with ammonia, but the yield of Va is inferior to that obtained by the reduction of benzoin oxime (4). In early experiments, a large excess of amine was used, and in fact was found necessary with volatile amines, since if only an exact equivalent of methylamine were used, the yield of Vb dropped by 15%. Later experiments showed that an amine excess of 10% was sufficient, and with non-volatile amines no excess was required.

The stereochemical aspects of this investigation were highly interesting. The stereospecificity of the reductive amination has been pointed out, and it might be mentioned that the by-product hydrobenzoin obtained in varying amounts was always the *meso* form, which is configurationally identical with the *erythro* aminoalcohols. It was found that many of these aminoalcohols formed crystalline penicillin salts which are only slightly soluble in water (*cf.* 6). The best of the series was found to be *levo-erythro*-1,2-diphenyl-2-methylaminoethanol (Vb), which forms a penicillin salt having a water solubility of about 0.1%. This penicillin salt has been recommended as an anti-allergenic preparation which elicits a very low percentage of untoward reactions in penicillin therapy (7). The dextrorotatory enantiomorph gives a penicillin salt which is approximately nine times as soluble; replacement of the methylamino by amino of other alkylamino groups invariably results in penicillin salts of greater water solubility. *Threo* isomers gave penicillin salts of greater solubility than the corresponding *erythro* compounds. In each case, penicillin salt formation could be utilized to effect a resolution of the racemic amine, as regeneration of the amine yielded an optically active amine. The difference in solubility of the two diastereoisomeric penicillin salts was usually sufficient to allow an effective separation of isomers by simply adding one equivalent of penicillin to two equivalents of the amine. This was accomplished by either a double decomposition reaction of potassium penicillin and the amine hydrochloride in water or direct salt formation from penicillinic acid and the amine in non-aqueous solvent. The availability of penicillin today in a high state of purity suggests that it should be considered as a possible resolving tool for racemic amines.

EXPERIMENTAL

Reaction of benzil with amines: α-alkyliminodesoxybenzoins. A mixture of 63.1 g. (0.3 mole) of benzil and 112 g. (0.9 mole) of 25% aqueous methylamine in 300 ml. of methanol was warmed to 50°, whereupon the benzil dissolved completely. On cooling crystallization pro-

ceeded rapidly, and 56.2 g. (84% yield) of α-methyliminodesoxybenzoin (IIb) was collected, m.p. 89.0–91.0°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.7; H, 5.9.
Found: C, 81.0; H, 6.0.

α-Isopropyliminodesoxybenzoin was prepared by allowing a mixture of 63.1 g. (0.3 mole) of benzil and 35.4 g. (0.6 mole) of isopropylamine in 100 ml. of methanol to stand at room temperature for five days with occasional shaking. At the end of one day, the benzil had dissolved completely and at the end of the fourth day the Schiff's base had begun to crystallize. There was obtained 72 g. (95% yield) of IId, m.p. 86.0–88.0°.

Anal. Calc'd for $C_{17}H_{17}NO$: C, 81.2; H, 6.8.
Found: C, 81.7; H, 6.9.

Similarly, 63.1 g. (0.3 mole) of benzil and 60.0 g. (0.6 mole) of cyclohexylamine yielded, after two days at room temperature, 81.7 g. (94% yield) of *α-cyclohexyliminodesoxybenzoin* (IIe), m.p. 79.0–82.0°.

Anal. Calc'd for $C_{20}H_{21}NO$: C, 82.7; H, 7.0.
Found: C, 82.3; H, 7.3.

A solution of 210 g. (1.0 mole) of benzil and 142 g. (1.1 moles) of 1,1,3,3-tetramethylbutylamine in 100 ml. of toluene was refluxed for six days, collecting water as formed in a trap. The oil remaining after evaporation of the solvent under reduced pressure was taken up in 500 ml. of Skellysolve A and a small amount of solid was removed by filtration. Distillation of the filtrate afforded 164 g. of IIh as a viscous oil, b.p. 161–165° at 1 mm., n_D^{26} 1.5637 (51% yield).

Anal. Calc'd for $C_{22}H_{27}NO$: C, 82.2; H, 8.5.
Found: C, 82.3; H, 8.5.

Reaction of benzoin with methylamine. Benzoin (21.2 g., 0.1 mole) and 37.2 g. (0.3 mole) of 25% aqueous methylamine were mixed together in 100 ml. of methanol and the mixture was warmed to 50°. A large amount of benzoin remained undissolved (with benzil a clear solution was obtained at this point). More methanol (100 ml.) was added and the mixture was stirred at reflux for 30 minutes. All of the solid had dissolved at the end of this time. On cooling, 8.6 g. of benzoin crystallized and was recovered on filtration (38% recovery). Evaporation of the solvent from the filtrate left a reddish oil from which no crystalline material could be obtained.

DL-*α-Methylaminodesoxybenzoin.* (IIIb). *Palladium-catalyzed reductive amination.* One gram of a 5% palladium-on-charcoal catalyst slurried with a little water was added to a mixture of 21.0 g. (0.1 mole) of benzil and 37.2 g. (0.3 mole) of 25% aqueous methylamine in 100 ml. of methanol. Hydrogenation was carried out at room temperature and at an initial pressure of 51 p.s.i. Hydrogen absorption stopped after 20 minutes, with a pressure drop corresponding to 94% of theory having occurred. The catalyst was removed and the filtrate was concentrated until two layers formed. To this residue was added 200 ml. of benzene and 100 ml. of 12 *N* hydrochloric acid, and the mixture was chilled with occasional stirring. The precipitated DL-α-methylaminodesoxybenzoin hydrochloride was collected, giving 23.4 g., m.p. 224–232° dec. (89% yield). One recrystallization from water narrowed the range to 227–232° dec.; further recrystallizations effected no improvement. [Lit. m.p. 216–220° dec. (13).]

DL-*α-Methylaminodesoxybenzoin* (IIIb). *Raney nickel-catalyzed reductive amination.* Benzil (42 g., 0.2 mole) and 74.4 g. (0.6 mole) of 25% aqueous methylamine were placed in a hydrogenation vessel with 200 ml. of methanol and 20 g. of Raney nickel.[2] Hydrogenation was started at an initial pressure of 52 p.s.i., and heat was applied so that the temperature of the reaction mixture was held at 45–50° during the reaction. After 35 minutes, a pressure drop corresponding to one equivalent of hydrogen had been noted and hydrogenation was

[2] The Raney nickel used throughout this investigation was used as purchased from the Gilman Paint and Varnish Works, Chattanooga, Tenn. The weights refer to the wet paste as received.

stopped. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure until two layers appeared. To the residue were added 150 ml. each of toluene and 12 *N* hydrochloric acid. Chilling and scratching induced crystallization. There was obtained 30.6 g. of DL-α-methylaminodesoxybenzoin hydrochloride, m.p. 224–232° dec. (58% yield). On standing, the filtrate deposited an additional 17.7 g. of slightly less pure material; total yield, 48.3 g. (91%). A mixture of this material with the product obtained from the palladium-catalyzed reduction melted at 224–232° dec.

DL-*erythro-1,2-Diphenyl-2-alkylaminoethanols: Reductive amination of benzil.* A typical example is given. About 20 g. of Raney nickel was added to a mixture of 42.0 g. (0.2 mole) of benzil and 74 ml. (0.6 mole) of a 33% methanolic solution of methylamine in 150 ml. of methanol and hydrogenation was initiated at 50 p.s.i. and at room temperature. Absorption of hydrogen was exothermic and rapid at first, but the rate decreased markedly after one equivalent of hydrogen had been absorbed. Heat was applied as required to maintain the temperature of the mixture at about 50°. After two hours a pressure drop corresponding to 94% of theory had occurred; hydrogenation was stopped. It was necessary to add 250 ml. of methanol and to heat to boiling to dissolve all the organic matter. The hot solution was filtered to remove catalyst and the methanol was distilled under reduced pressure. The semi-solid residue was taken up in 250 ml. of warm toluene and was stirred with 250 ml. of 4 *N* hydrochloric acid. After the mixture had been thoroughly chilled, the precipitated DL-erythro-1,2-diphenyl-2-methylaminoethanol hydrochloride was collected. On recrystallization from water, there was obtained 37.9 g. of Vb·HCl, m.p. 254–255° dec.; a second crop of 8.3 g., m.p. 252–254° dec., came out on concentration of the mother liquor (total yield 88%). The toluene layer of the original filtrate was dried and evaporated to dryness. A residue of 1.5 g. remained. Subsequent experiments showed that this neutral material is largely *meso*-hydrobenzoin. The amount of catalyst may be reduced, but the rate of hydrogenation decreases as a result. Hydrogenation at high pressures (500–1000 p.s.i.) gives Vb in yields of the same order.

Those aminoalcohols which were isolated as the free base (see Table I) were obtained by chilling the methanol filtrate after the catalyst had been removed. The *erythro*-1,2-diphenyl-2-alkylaminoethanols are characterized by limited solubility in organic solvents, and only slight solubility of the hydrochlorides in water. This behavior complicated isolation and purification in those reactions in which an appreciable amount of hydrobenzoin was formed (notably those in which benzoin was the starting material), since the solubility of hydrobenzoin in organic solvents is likewise limited.

DL-*erythro-1,2-Diphenyl-2-methylaminoethanol* (Vb): *Hydrogenation of* IIIb. One-tenth mole (26.2 g.) of the hydrochloride of DL-α-methylaminodesoxybenzoin (IIIb) was shaken with dilute alkali and the liberated aminoketone was extracted with four portions of ether. The ether extracts were combined, shaken with saturated sodium chloride, filtered through potassium carbonate, and the solvent evaporated on the steam-bath. The residual oil was taken up in 200 ml. of methanol, Raney nickel (10 g.) was added, and hydrogenation was started at 51 p.s.i. After 25 minutes a pressure drop corresponding to 89% of theory had occurred. The catalyst was removed and the filtrate concentrated until crystallization began. On chilling and filtering, 15.0 g. of Vb was obtained, m.p. 135.0–138.0°. Pouring the filtrate into 500 ml. of water gave an additional 5.9 g. of less pure material, m.p. 123.0–135.0° (total yield, 92%).

DL-*erythro-1,2-Diphenyl-2-methylaminoethanol: Hydrogenation of* IIb. One-tenth mole (22.3 g.) of IIb was suspended in 100 ml. of methanol, 10 g. of Raney nickel was added, and hydrogenation was initiated at 51 p.s.i. and at room temperature. The absorption of hydrogen was rapid and exothermic. After 12 minutes, a pressure drop corresponding to 89% of theory for two equivalents of hydrogen had occurred. During the reduction, the Schiff's base dissolved completely, and then crystallization of Vb began. Apparently the crystals occluded the catalyst particles, as hydrogenation ceased abruptly. Shaking was stopped, 150 ml. of methanol was added, and the suspension was warmed to cause the product to dissolve. After removal of the catalyst, the filtrate was concentrated to a volume of about 100 ml. On cooling, crystals separated and were collected. There was obtained 18.7 g. (82%

yield) of Vb, m.p. 135.5–138.0°. By pouring the filtrate into a liter of water, an additional 2.3 g. of slightly less pure product separated. When hydrogenation was interrupted after one equivalent of hydrogen had been absorbed, the resulting product appeared to be a mixture of Vb and unchanged starting material.

DL-*erythro-1,2-Diphenyl-2-methylaminoethanol* (Vb). *Reductive amination of benzoin.* In an experiment using 21.2 g. (0.1 mole) of benzoin, 8.5 g. (0.11 mole) of 40% aqueous methylamine, and 5 g. of Raney nickel, five hours' hydrogenation at about three atmospheres was required to attain 89% of the theoretical uptake of hydrogen. This experiment gave 14.6 g. (55% yield) of Vb, 6.0 g. (28% yield) of *meso*-hydrobenzoin, and 3.5 g. of impure neutral residual material. As with benzil, high pressure hydrogenation gave results comparable to those obtained at low pressure. The use of more catalyst, a larger excess of methylamine, or heating the methylamine and benzoin together prior to hydrogenation failed to improve the yield of Vb significantly.

TABLE I

PREPARATION OF $C_6H_5CH(OH)—CHC_6H_5$ (NHR)

CPD. NO.	R	AMINE: BENZIL	TIME, hours	YIELD, %	M.P., °C. of base	M.P., °C. of hydrochloride	WORKUP	FORMULA	CARBON		HYDROGEN	
									Calc'd	Found	Calc'd	Found
Va	H	6:1[a]	17	56	165–166	240–241	*e*	*h*				
Vb	CH_3	3:1	2	88	135.5–138	254–255	*e*	*i*				
Vc	C_2H_5	2:1[b]	4	78	138.5–140	256	*e*	$C_{16}H_{19}NO\cdot HCl$	68.9	69.4	7.6	7.1
Vd	$CH(CH_3)_2$	2:1	4	65[c]	150–153	255	*f*	$C_{17}H_{21}NO$[d]	80.0	80.1	8.3	8.4
Ve	C_6H_{11}	2:1	6	64[c]	165–167	231–233	*f*	*j*				
Vf	$CH_2C_6H_5$	2:1	5	40[g]		229	*e*	*k*				
Vg	*n*-$C_{12}H_{25}$	1:1	26	61	108–110	138–142.5	*f*	*l*				
Vh	*tert*-C_8H_{17}	1:1	23	23[c]		211.5–212	*e*	$C_{22}H_{31}NO\cdot HCl$	73.0	72.8	8.9	9.0
Vi	CH_2CH_2OH	2:1	19	94	107–108.5	239–242	*e*	*m*				
Vj	$CH_2CH_2NC_4H_8O$	4:3	7	41		243.5–246	*e*	$C_{20}H_{26}N_2O_2\cdot 2HCl$	59.3	59.1	7.3	7.2
Vk	$CH_2CH_2N(C_2H_5)_2$	2:1	13	63	105–107		*f*	$C_{20}H_{28}N_2O$	76.9	77.2	9.0	8.8

[a] Ammonium hydroxide (28%) used. [b] Aqueous ethylamine (33%) used. [c] These were prepared by isolation of the Schiff's bases and subsequent reduction; yields are over-all, based on benzil. The usual reductive amination procedure resulted in high recoveries of *meso*-hydrobenzoin. [d] *Hydrochloride:* Calc'd for $C_{17}H_{21}NO\cdot HCl$: C, 70.0; H, 7.6; Found: C, 70.0; H, 7.7. [e] Product isolated as hydrochloride. [f] Product isolated as free base. [g] The absorption of hydrogen exceeded theory; it is probable that some debenzylation occurred. [h] Lit. m.p. 165–166° base (5); 233–234° (5), 219–220° (4) hydrochloride. [i] Lit. m.p. 136–137° (6) base; 270–271° (6), 250° (9) hydrochloride. [j] Lit. m.p. 163–164° (5) base; 239–240° (5), 264–265° (9) hydrochloride. [k] Lit. m.p. 154–155° (5) base; 228–229° (5) hydrochloride. [l] Lit. m.p. 112–114° (5) base; 145.5–148° (5) hydrochloride. [m] Lit. m.p. 105–105.5° (5) base; 237–238.5° (5) hydrochloride.

Hydrogenation of benzil. Low pressure hydrogenation of benzil in methanol over Raney nickel at 50° proceeds rather slowly, requiring 1.5 hours for absorption of one equivalent and 5 hours for absorption of two equivalents of hydrogen. After one equivalent is absorbed, benzoin may be isolated in good yield; after two equivalents, *meso*-hydrobenzoin (*cf.* 14). By comparison, the reaction of benzil with methylamine is virtually complete in a few minutes.

Penicillin salts of dextro- and levo-erythro-1,2-diphenyl-2-methylaminoethanol. Potassium benzylpenicillinate (3.7 g., 0.01 mole) was shaken with 50 ml. of ether and 20 ml. of 8.5% phosphoric acid until two clear layers resulted. The aqueous layer was discarded and the ether layer was washed once with 20 ml. of cold water. The ether solution of benzylpenicillinic acid was added all at once to a solution of 4.1 g. (0.018 mole) of DL-Vb in 300 ml. of ether. An immediate precipitation of solid occurred. After five minutes the solid was collected and air-dried. It amounted to 4.7 g. and melted with decomposition at 174–176°. Recrystallization by dissolving in dimethylformamide and diluting with ether raised the

melting point to 182.5–183.5° dec.; lit. 186–188° (6). Regeneration of *levo*-Vb by shaking a portion of the penicillin salt with dilute alkali and ether, separating the ether layer and evaporating the solvent yielded the levorotatory enantiomorph of Vb, $[\alpha]_D^{25}$ −34.4°.[3]

The ether filtrate containing *dextro*-Vb was treated with an ether solution of benzylpenicillinic acid prepared from 7.4 g. (0.02 mole) of potassium benzylpenicillinate in a manner similar to that described above. A gum separated at first, which slowly solidified on rubbing with a stirring rod. The crude penicillin salt was collected. It amounted to 4.2 g., and melted at 142.0–145.0°; lit. 148–151° (6). The dextrorotatory enantiomorph regenerated from this salt had the specific rotation +35.1°. The rotations recorded in the literature are −40.0° and +38.2° for these enantiomorphs; resolution was thus about 90% effective. Our purified samples of *levo*- and *dextro*-Vb and penicillin salts thereof possessed melting points and specific rotations in excellent agreement with values given by Young. The constants for the hydrochlorides do not agree however. For comparison, these values are tabulated in Table II. The *levo*-Vb penicillin salt is prepared equally as well from potassium benzylpenicillinate and DL-Vb hydrochloride in water (*cf.* 6). The greater (0.9% as compared to 0.1%) water solubility of the *dextro*-Vb penicillin salt makes it desirable to isolate the unreacted *dextro*-Vb from the aqueous filtrate and to treat it in ether with benzylpenicillinic

TABLE II

COMPARISON OF PHYSICAL CONSTANTS FOR OPTICAL ISOMERS OF *erythro*-1,2-DIPHENYL-2-METHYLAMINOETHANOL HYDROCHLORIDES

COMPOUND	DATA OF YOUNG (6)		DATA OF THIS WORK	
	m.p., °C.	$[\alpha]_D^{25}$	m.p., °C.	$[\alpha]_D^{25}$
DL-Vb·HCl	270.0–271.0		254.0–255.0	
levo-Vb·HCl	297.0–297.5	−80.6	268.5–269.5	−145
dextro-Vb·HCl	295.0–296.0	+78.7	268.0–269.5	+144

acid. Compounds Va, Vc, and Vf gave crystalline penicillin salts by analogous procedures. In each case, the aminoalcohol regenerated from the penicillin salt was optically active.

SUMMARY

The reductive amination of benzil with primary amines over Raney nickel, at either low or high pressure, offers a convenient preparation of DL-*erythro*-1,2-diphenyl-2-alkylaminoethanols; traces of the *threo* racemates cannot be detected. The experimental facts are consistent with a mechanism involving the initial formation of a Schiff's base (II) from benzil and the amine, followed by hydrogenation to the aminoalcohol (V). With primary carbinamines, *e.g.*, methylamine, hydrogenation of a mixture of benzil and the amine is quite satisfactory; with secondary carbinamines, *e.g.*, isopropylamine, it is preferable to allow the amine and benzil to react prior to hydrogenation.

Replacement of benzil by benzoin results in lower yields of the aminoalcohol and a considerable amount of *meso*-hydrobenzoin.

A number of the DL-*erythro*-1,2-diphenyl-2-alkylaminoethanols form sparingly-soluble crystalline salts with penicillin, effecting a resolution of the racemic amine thereby.

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[3] All specific rotations refer to $c = 1$ in methanol.

BIBLIOGRAPHY

(1) DODDS, LAWSON, AND WILLIAMS, *Nature*, **151**, 614 (1943); *Proc. Roy. Soc. (London)*, **B132**, 119 (1944).
(2) DODDS, LAWSON, SIMPSON, AND WILLIAMS, *J. Physiol. (London)*, **104**, 47 (1945).
(3) HOLCK, KIMURA, AND KIMURA, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 354 (1950).
(4) WEIJLAND, PFISTER, SWANEZY, ROBINSON, AND TISHLER, *J. Am. Chem. Soc.*, **73**, 1216 (1951).
(5) LUTZ, FREEK, AND MURPHEY, *J. Am. Chem. Soc.*, **70**, 2015 (1948).
(6) YOUNG, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 261 (1951).
(7) LONGACRE, *Antibiotics & Chemotherapy*, **1**, 223 (1951); KADISON, *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **12**, 327 (1951).
(8) EMERSON, in ADAMS, *Org. Reactions*, **4**, 174 (1949).
(9) SKITA AND KEIL, *Ber.*, **62**, 1142 (1929).
(10) SKITA, KEIL, AND BAESLER, *Ber.*, **66**, 858 (1933).
(11) CAMERON, NIXON, AND BASTERFIELD, *Trans. Roy. Soc. Can.*, III [3] **25**, 145 (1931).
(12) JULIAN, MEYER, MAGNANI, AND COLE, *J. Am. Chem. Soc.*, **67**, 1203 (1945).
(13) GOODSON AND MOFFETT, *J. Am. Chem. Soc.*, **71**, 3219 (1949).
(14) BUCK AND JENKINS, *J. Am. Chem. Soc.*, **51**, 2163 (1929).