a hapten as benzenesulfonic acid (possibly slightly weaker), in agreement with observation.

Dimethylarsinic acid was observed to have only very small combining power with the antisera.

The Action of Other Arsenic Compounds.—No inhibition was observed with *p*-aminophenylarsine oxide, phenyldimethylarsine dihydroxide, or phenyldimethylarsine hydroxybromide. (The last two substances probably produce the same ion in solution.)

Hapten Inhibition of Precipitation of Anti-R_{CH_3} Serum.—Phenylmethylarsinic acid, the homologous substance to anti-R_{CH_3} serum, combines more strongly with it than any other hapten tested. The arsonic acids and phenylphosphonic acid were found to combine only very weakly with this antiserum. Replacing the methyl group by a hydroxyl group greatly decreases the combining power of the hapten. It is interesting that methylarsonic acid combines with the antiserum as strongly as does phenylarsonic acid, which can exert a much greater van der Waals attraction.

This investigation was carried out with the aid of a grant from The Rockefeller Foundation. We wish to thank Mr. Dan Rice for assistance in analyses.

Summary

Quantitative studies have been made of the inhibiting power of various haptens (including arsenic acid, methylarsonic acid, dimethylarsinic acid, benzylarsonic acid, phenylarsonic acid, phenylmethylarsinic acid, phenylphosphonic acid, benzenesulfonic acid, and phenylstibonic acid) on the precipitation of anti-*o*-, anti-*m*-, and anti-*p*-azophenylarsonic acid sera, anti-*p*-(*p*-azophenylazo)-phenylarsonic acid serum, and anti-*p*-azophenylmethylarsinic acid serum with hapten-homologous azoproteins and (for two antisera) with a dihaptenic azo-dye. The results are discussed in relation to the structure of the molecules.

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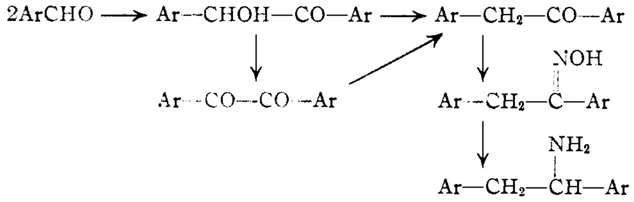
Some α,β-Diphenylethylamines[1,2]

BY JONATHAN L. HARTWELL AND SYLVIA R. L. KORNBERG

The report of Lettré and co-workers[3] that α,β-diphenyl-ethylamines substituted in one of the phenyl groups by at least one methoxyl group possess the ability to inhibit the mitosis of certain cells in tissue culture prompted the inclusion of this type of compound in a systematic study of the action of chemical agents on mammalian cancer. The present paper describes the preparation and properties of several of these compounds and their intermediates. The biological results, obtained in collaboration with other workers on this joint project,[2] will be reported elsewhere.

The method of synthesis chosen for most readily obtaining a variety of alkoxyl-substituted α,β-diphenylethylamines was the benzoin condensation of alkoxybenzaldehydes followed usually by reduction to the desoxybenzoin, oximation, and finally reduction, as outlined by the formulas



In this work many compounds not new to the literature were prepared, but the present paper reports only the new compounds and new observations deemed of interest. New benzoins were prepared in the usual manner from 2,3-dimethoxy-, 2,5-dimethoxy- and 3,4,5-trimethoxybenzaldehyde. The failure of benzoin formation in the cases of 2,4- and 3,5-dimethoxybenzaldehyde is to be noted. Desoxybenzoins were produced directly by reduction of all the benzoins with the exception of 2,5,2′,5′-tetramethoxybenzoin, veratroin and 3,4,5,3′,4′,5′-hexamethoxybenzoin. Of these the last was obtained crystalline but in too small yield for further preparative work. The first two failed to crystallize, but the crude products were oxidized to the benzils. Desoxyveratroin was then obtained from veratril by reduction; not enough of the other benzil was available for further work. The oximation of our desoxybenzoins appeared to give one

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[1] Paper XI in the series entitled "Chemical Treatment of Tumors." Paper X in this series: Brues and Shear, *J. Nat. Cancer Inst.*, **5**, 195 (1944).

[2] Material contained in this paper was presented, in part, at the A. A. A. S., Gibson Island Conference on Cancer at Gibson Island, Maryland, on August 3, 1945, as one of the contributions in the symposium entitled "Some Aspects of a Joint Institutional Research Program on Chemotherapy. Current Laboratory and Clinical Experiments with Bacterial Polysaccharide and with Synthetic Compounds," by Shear, Hartwell, Peters, Dalton, Diller, Royle, Holloman, Oakey, Rees, Hauschke, Dunn and Reimann.

[3] Lettré, Albrecht and Fernholz, *Naturwissenschaften*, **29**, 390 1941); Lettré and Fernholz, *Z. physiol. Chem.*, **278**, 175 (1943).

geometrical isomer in almost every case, judging by yields and purity of the oximes; in this, our experience confirms the more extensive work of Buck and Ide.[4] However, in the case of 2,3-dimethoxybenzyl-2,3-dimethoxyphenyl-ketoxime, both isomers were isolated. The oximes were smoothly reduced to amines by sodium amalgam and alcohol. They were isolated as free bases when crystalline, and as hydrochlorides and picrates when not crystalline.

Experimental

Aldehydes.—2,3-Dimethoxybenzaldehyde and 2,4-dimethoxybenzaldehyde were purchased from a commercial source. *m*-Methoxybenzaldehyde, 3,5-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde were prepared by the Rosenmund reduction of the acid chlorides.[5] The latter were prepared in the usual manner from the acids and thionyl chloride. 3,5-Dimethoxybenzoic acid was obtained by methylating[6] the dihydroxy acid.[7] 2,5-Dimethoxybenzaldehyde was prepared by the persulfate oxidation of salicylaldehyde,[8] followed by methylation.[9]

Benzoins (Table I).—The benzoin condensations were carried out in a manner similar to the general procedure of Dewar and Read.[10] The benzoin from 2,5-dimethoxybenzaldehyde resisted efforts at crystallization, but was successfully used in a crude state for oxidation to the benzil. Attempts to induce 2,4- and 3,5-dimethoxybenzaldehyde to undergo the benzoin condensation were unsuccessful; oxidation of the crude reaction mixtures did not result in the formation of the corresponding benzils.

Benzils (Table I).—The benzils were prepared from the benzoins by the method given in "Organic Syntheses" for benzil.[11]

The benzil described by Staudinger, *et al.*,[12] as the 2,3,2′-3′-tetramethoxy derivative, m. p. 214°, as well as their "2,3,2′,3′-tetramethoxybenzophenone" m. p. 145°, appear to be incorrectly named and formulated. These errors have been perpetuated in "Stelzner."[13] Obviously, the 3,4,3′,4′-derivatives were meant in each case. Both were obtained as products in the Friedel–Crafts reaction of oxalyl chloride with veratrole; the benzophenone derivative had been recorded before,[14] and veratril was well-known.[15] 2,3,2′,3′-Tetramethoxybenzil was prepared unambiguously by us and found to melt at 144.9–145.4° (cor.).

Desoxybenzoins (Table I).—Benzoins, with the exception of veratroin, were reduced smoothly to desoxybenzoins by the tin–copper couple.[16] In practice, 30-mesh granulated tin and a solution of hydrated copper sulfate in concentrated hydrochloric acid containing 1.0 g. of the salt in 35 cc. of the acid were employed. With veratroin, however, the desoxy derivative could not be isolated from the reaction mixture; in this case, desoxyveratroin was prepared from veratril.[16]

An attempt was made to reduce piperoin by the tin-mercury couple, a method used successfully with benzoin.[17] Only a dark tar was obtained, and further attempts were abandoned since the procedure of Allen and Buck was satisfactory.

A method using zinc dust and alkali, recommended[18] for the reduction of ortho-substituted benzoins, was carried out with 2,2′-dimethoxybenzoin and was found to be inferior to the first method; a lower yield of a less pure product was obtained.

The reduction of *p*-methoxybenzoin, m. p. 105.6–106.4° (cor.), was found by us to yield both possible isomeric desoxy compounds each in substantial quantity. This supplements the work of Buck and Ide,[4] who isolated one isomer. The crude mixture, obtained in 97% yield, was submitted to a rather long crystallization procedure from alcohol, and two pure compounds were isolated, the less soluble melting at 95.2–96.2° (cor.)[19] and the more soluble melting at 75.7–76.7° (cor.).[20] Their oximes melted, respectively, at 131.5–133.0° (cor.)[19] and 116.3–117.9° (cor.).[20]

Desoxybenzoinoximes (Table I).—The general procedure for preparing the oximes was to heat the desoxybenzoins with hydroxylamine hydrochloride in pyridine,[16] and all but 3,3′-dimethoxydesoxybenzoin oxime (compound 9, Table I) were prepared in this manner. This oxime was prepared satisfactorily by refluxing the ketone with hydroxylamine hydrochloride and sodium acetate in alcohol. 2,3,2′,3′-Tetramethoxydesoxybenzoin oxime (compounds 10 and 11, Table I) and benzyl 3,4-methylenedioxyphenyl ketone oxime were also prepared by this method as well as by the pyridine method; with the former, the sodium acetate method resulted in a higher yield of product of equal purity while with the latter this method gave a product of lower purity in lower yield. The best sample of benzyl 3,4-methylenedioxyphenyl ketone oxime melted at 106.8–107.8° (cor.).[21]

It was the experience of Buck and Ide[4] as well as our own, that oximation of desoxybenzoins resulted usually in only one product. In the case of 2,3,2′,3′-tetramethoxydesoxybenzoin oxime the following evidence suggests that both geometrical isomers were formed. The crude oxime was obtained in 79% yield, m. p. 76.5–79.5° (cor.). Repeated crystallization from different solvents gave a small yield of a pure oxime melting constantly at 100.9–101.8° (cor.). When the mother liquors were all combined and subjected to reduction, the expected amine and a compound melting constantly at 125.8–126.4° (cor.) were obtained. The latter compound separated from the reaction mixture in 14% yield before neutralization of the acid solution. It, however, gave analytical values for the oxime. The lower melting oxime was slightly soluble in hot dilute sodium hydroxide solution, while the higher melting compound was no more soluble in this reagent than in hot water. It is suggested that the difficultly purifiable crude oxime consisted of both geometrical isomers which differed in their ease of reduction to the amine, hindrance being offered by the higher melting isomer to reduction as well as to solution in alkali.

α,β-Diphenylethylamines (Table II).—The procedure followed for the reduction of the oximes was that of Allen and Buck[16] except that we used 3 instead of 3.5% sodium amalgam, and added the amalgam in two portions rather than in one. In all the cases reported here the free bases could not be obtained crystalline; the hydrochlorides, however, were obtained crystalline as colorless needles by adding the theoretical quantity of concentrated hydrochloric acid to the solution of the free base in absolute

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[4] Buck and Ide, This Journal, **53**, 1536 (1931).

[5] Hershberg and Cason, "Organic Syntheses," **21**, 84 (1941). *m*-Methoxybenzaldehyde has not hitherto been reported as having been prepared by this method.

[6] Bülow and Riess, *Ber.*, **35**, 3901 (1903); Mauthner, "Organic Synthesis," Coll. Vol. I, 2nd ed., 1941, p. 357.

[7] Weston and Suter, "Organic Synthesis," **21, 27** (1941).

[8] Neubauer and Flatow, *Z. physiol. Chem.*, **52**, 382 (1907).

[9] Hodgson and Beard, *J. Chem. Soc.*, 2339 (1927).

[10] Dewar and Read, *J. Soc. Chem. Ind.*, **55**, 347 (1936).

[11] Clarke and Dreger, "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p. 87.

[12] Staudinger, Schlenker and Goldstein, *Helv. Chim. Acta*, **4**, 341 (1921).

[13] Stelzner, "Literatur-Register der organischen Chemie," 1919, 1920 and 1921.

[14] v. Kostanecki and Tambor, *Ber.*, **39**, 4027 (1906); m. p. 145°. Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1661 (1906); m. p. 144°.

[15] Fritsch, *Ann.*, **329**, 54 (1903), m. p. 219–220°.

[16] Allen and Buck, This Journal, **52**, 312 (1930).

[17] Ballard and Dehn, *ibid.*, **54**, 3970 (1932).

[18] LaForge, *ibid.*, **55**, 3040 (1933).

[19] Ref. 4: *p*-methoxybenzyl phenyl ketone, m. p. 96°; oxime, m. p. 133°.

[20] Torrès and Gonzalès, *Bull. soc. chim.*, **37**, 1591 (1925): benzyl *p*-methoxyphenyl ketone, m. p. 77°; oxime, m. p. 114°. Jenkins, This Journal, **55**, 703 (1933): ketone, m. p. 77° (cor.); oxime, m. p. 118.5° (cor.).

[21] Melting point 103°, ref. 4.

TABLE I

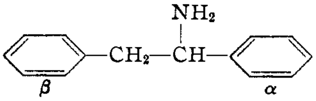
INTERMEDIATE COMPOUNDS

Compound	Name	Appearance, cryst. solv.	M. p., °C. (cor.)	Yield, crude, %	Empirical formula	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Benzoin						
1	2,3,2',3'-Tetramethoxy-	Colorless prisms, alc. or MeOH	86.0–87.3	44	$C_{18}H_{20}O_6$	65.1	65.1	6.1	6.2
2	2,5,2',5'-Tetramethoxy-	Yellow oil[d]	....	100	......	..	..	...	...
3	3,4,5,3',4',5'-Hexamethoxy-	Pale yellow prisms, alc.	147.5–148.6	16	$C_{20}H_{24}O_8$	61.2	61.5	6.2	6.5
			Benzil						
4	2,3,2',3'-Tetramethoxy-	Pale yellow prisms, alc.	144.9–145.4	100	$C_{18}H_{18}O_6$	65.5	65.9	5.5	5.6
5	2,5,2',5'-Tetramethoxy-	Pale yellow prisms, alc.	153.9–155.1	50	$C_{18}H_{18}O_6$	65.5	65.3	5.5	5.7
			Desoxybenzoin						
6	3,3'-Dimethoxy-[b]	Pale yellow oil	........[e]	75	$C_{16}H_{16}O_3$	75.0	75.5	6.3	6.3
7	2,3,2',3'-Tetramethoxy-	Colorless plates, alc.	57.5–58.5	78	$C_{18}H_{20}O_5$	68.4	68.3	6.4	6.5
			Desoxybenzoin oxime						
8	2,2'-Dimethoxy-[c]	Colorless prisms, alc.	108.7–110.3	80	$C_{16}H_{17}NO_3$	70.8	70.9	6.3	6.5
9	3,3'-Dimethoxy-	Colorless prisms, alc.	102.1–102.9	84	$C_{16}H_{17}NO_3$	70.8	70.8	6.3	6.6
10	2,3,2',3'-Tetramethoxy-	Colorless prisms; 70% alc., MeOH, or ether + hexane	100.9–101.8	79	$C_{18}H_{21}NO_5$	65.2	65.2	6.4	6.5
11	2,3,2',3'-Tetramethoxy-	Colorless prisms, alc.	125.8–126.4		$C_{18}H_{21}NO_5$	65.2	65.5	6.4	6.4[f]

[a] All analyses reported in this paper are by Arlington Laboratories, Fairfax, Virginia. [b] Prepared from the corresponding benzoin, m. p. 52.8–55.5° (cor.), of Schönberg and Malchow, *Ber.*, **55**, 3752 (1922). [c] Prepared from the corresponding desoxybenzoin, m. p. 53.3–54.8° (cor.), of LaForge (ref. 28). [d] Not purified. [e] Boiling point 233–236° at 6 mm. [f] Also: calcd. for N: 4.2; found: 4.4; calcd. for Cl: 0.0; found, 0.0.

TABLE II

ALKOXY α,β-DIPHENYLETHYLAMINES,



Compound	Substituents on α-Phenyl	Substituents on β-Phenyl	Derivative	M. p., °C. cor.	Yield, crude, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
12	2-Methoxy	2-Methoxy	Hydrochloride[e]	193.0–196.0	53[g]	$C_{16}H_{20}ClNO_2$	65.4	65.2	6.9	7.0	4.8	4.4
13	3-Methoxy	3-Methoxy	Hydrochloride[h]	194.5–195.6	83	$C_{16}H_{20}ClNO_2$	65.4	65.6	6.9	6.9	4.8	4.7
14	3-Methoxy	3-Methoxy	Picrate[h]	185.0–185.6	47[b]	$C_{28}H_{26}N_7O_{16}$	47.0	47.7	3.5	3.8	13.7	13.7
15	2,3-Dimethoxy	2,3-Dimethoxy	Hydrochloride[h]	166.2–168.2	90[c,g]	$C_{18}H_{24}ClNO_4$	61.1	60.8	6.8	6.9	4.0	4.0
16	2,3-Dimethoxy	2,3-Dimethoxy	Picrate[f]	220.7–223.0	49[d]	$C_{24}H_{26}N_4O_{11}$	52.7	53.3	4.8	4.8	10.3	10.5
17[a]	3,4-Methylenedioxy	None	Hydrochloride[h]	247.0–248.4	63[g]	$C_{15}H_{16}ClNO_2$	64.9	64.5	5.8	5.9	5.0	4.9

[a] Prepared from benzyl 3,4-methylenedioxyphenyl ketone oxime, m. p. 106.8–107.8° (cor.), of Buck and Ide (ref. 4). [b] Based on hydrochloride; yellow needles. [c] Based on picrate. [d] Based on oxime; yellow prisms. [e] Hydrochloride crystallized from alcohol and ether. [f] Picrate crystallized from *n*-butanol. [g] Colorless needles. [h] Crystallized from alcohol.

alcohol. With amines 13 and 15 (Table II), a pure hydrochloride could not be obtained in this manner alone; purification was accomplished by preparation of the pure picrates as yellow needles, decomposition by alkali, extraction of the free base and formation of the hydrochlorides as above. The low yield of the picrate of α,β-di-(3-methoxyphenyl)-ethylamine (compound 14) (47%) was due to the employment of an insufficient amount of picric acid; the theoretical quantity of picric acid for the mono picrate had been used on the whole batch before receipt of the analytical results which showed that 2 molecules of picric acid were required. The low yield of the picrate of α,β-di-(2,3-dimethoxyphenyl)-ethylamine (compound 16) may have been due to incomplete reduction of the oxime, a subject which is discussed in the preceding section on oximes.

The amine hydrochlorides reported in Table II were all quite soluble in water.

Summary

1. The synthesis and properties of several new alkoxy α,β-diphenylethylamines and their intermediates, prepared in the course of studies in the chemotherapy of cancer, are reported.

BETHESDA, MARYLAND

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