Anal. Calcd. for $C_{34}H_{24}O_2$ (464.5): C, 87.9; H, 5.2. Found: C, 87.4, 87.4; H, 5.4, 5.2; mol. wt., 467.

1,2,2,3,4-Pentaphenyl-1-hydroxy-1,2-dihydronaphthalene, XI, m. p. 196.5–197.5°.—This white compound was formed in 98% yield from the reaction of phenyllithium on IX. Oxidation of 1.5 g. of XI by boiling for five minutes with 1.5 g. of chromium trioxide in 10 ml. of glacial acetic acid gave only a pinkish oil from which a small amount of benzophenone could be isolated as the 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{40}H_{30}O$ (526.6): C, 91.2; H, 5.7. Found: C, 90.4, 89.9; H, 5.9, 6.2; mol. wt., 520.

Summary

The reactions of 2,3-diphenyl-1,4-naphthoquinone with phenylmagnesium bromide and phenyllithium have been studied.

Structures have been proposed for the main products of these reactions and for the compound which results from the dehydration of both of them.

Five new compounds are described.

An improved method is described for the preparation of 2,3-diphenyl-1,4-naphthoquinone in three steps from 2,3-diphenyl-1-keto-1,2,3,4-tetrahydronaphthalene in 60% over-all yield.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Amines Related to 2,5-Dimethoxyphenethylamine. IV. 2,5-Diethoxy, 2-Hydroxy-5-methoxy and 2-Hydroxy-5-ethoxyphenylalkanolamines[1]

BY WALTER S. IDE AND RICHARD BALTZLY

In continuation of our studies on this interesting family of pressors, we report the preparation of the primary and secondary β-hydroxy-β-(2,5-diethoxyphenyl)-ethylamines and isopropylamines, and their analogs having hydroxyl groups in the 2-position with methoxyl or ethoxyl groups in the 5-position.

The 2,5-diethoxy family (I–IV) was prepared by a line of synthesis shown in the upper part of Chart I. In the main, this approach resembles that used in Paper II[2] of this series to prepare the corresponding dimethoxy compounds. The 2,5-diethoxyphenylalkanolamines and their precursors tend to be more soluble and less readily crystallized than their methoxy analogs and were usually isolated in lower yield.

The preparations of the 2-hydroxy-5-alkoxyphenylalkanolamines (V–XII) largely followed the scheme used in Paper III of this series[3] for the 2-hydroxy-5-methylphenylalkanolamines. These syntheses are outlined in the lower part of Chart I. A few comments are in order.

In the first preparation of the aminoalcohol VII, the isonitrosoketone VIIb was reduced directly with platinum in ethanolic hydrogen chloride solution. Compound VII was obtained without difficulty although it later became apparent that other substances were present in the mother liquors. In a later preparation, palladized charcoal was used for the first stage of the reduction and the 2-benzyloxyaminoketone hydrochloride, VIIa, was isolated as the major product. It is rather surprising that the 2-benzyl group was retained in the presence of this catalyst; the only rational explanation is that the sample of palladized charcoal had been partially inactivated. Successive hydrogenations of VIIa with fresh palladized charcoal and with platinum yielded VII.

In the preparation of Compound IX, the usually reliable hexamethylenetetramine method broke down, only traces of chloroform-insoluble material being obtained from the reaction of hexamethylene tetramine and IXc.[4] The bromoketone was then treated with benzhydrylamine[5] but apparently considerable tertiary as well as secondary amine was formed and the desired product was not readily separated. The synthesis of IX was finally accomplished by treating IXc with dibenzylamine. The reaction was slow and far from quantitative (in contrast to similar reactions with benzylmethylamine) but the tertiary amine IXb was isolated easily. On hydrogenation with palladized charcoal, IXb absorbed two mols of hydrogen rapidly at room temperature and a third more slowly at 65°.[6]

At the time this work was started, attempts were made to prepare amino alcohols having the

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group in the same laboratories.

(2) Baltzly and Buck, THIS JOURNAL, **62**, 164 (1940).

(3) Ardis, Baltzly and Schoen, *ibid.*, **68**, 591 (1946).

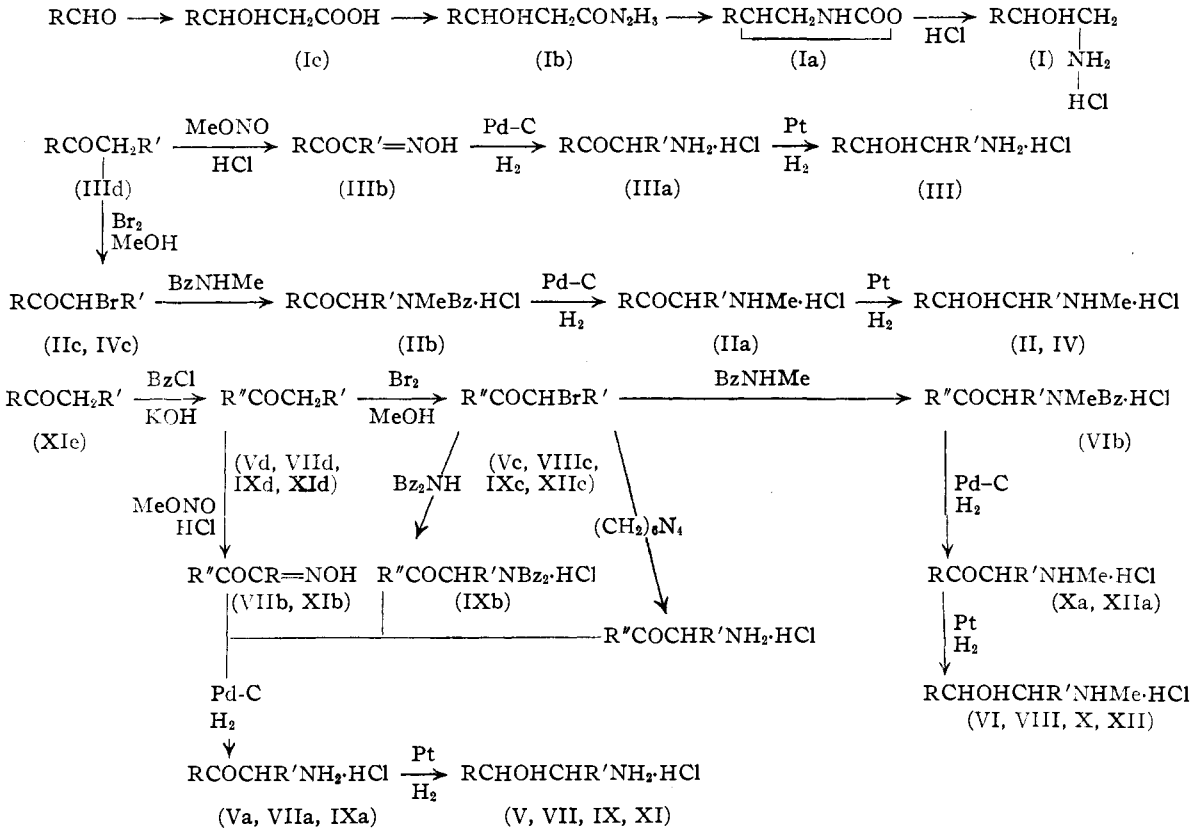
(4) Although this bromoketone is not especially active the failure of the preparation cannot be attributed to sluggishness since IXc reacts with reasonable speed with benzylmethylamine, benzhydrylamine and dibenzylamine. We are inclined to suspect that the initial reaction product was relatively soluble in chloroform and was accordingly exposed to the further reactions with bromoketone that should be possible from the conventional formula for hexamethylenetetramine but which are usually avoided by the precipitation of the first reaction-product. In the work reported in Paper III of this series it was found that if the temperature in a hexamethylenetetramine reaction was above 30–40°, the usual reaction product sometimes failed to precipitate. The original paper on this method as applied to phenacyl halides (Mannich and Hahn, *Ber.*, **44**, 1542 (1911) states that the reactions were carried out at room temperature but gives no indication that this condition is essential.

(5) *Cf.* Suter and Ruddy, THIS JOURNAL, **66**, 747 (1944).

(6) *Cf.* Simonoff and Hartung, *J. Amer. Pharmaceutical Assoc.*, **35**, 306 (1946). Obviously, this method involves a cleavage of benzylphenacylamine. It has gradually become apparent that although the benzyl group is usually removed preferentially from benzylphenacyl, benzyl β-hydroxyphenethyl and benzyl phenethylamines, these other groups have considerable labilizing effect, cleavage being achieved under conditions comparable with those required for cleavage of dibenzylamines.

CHART I

The numbers are those of new substances isolated in pure form: Bz = benzyl; R = 2,5-diethoxyphenyl for I, II, III, IV; R = 2-hydroxy-5-methoxyphenyl for V, VI, VII, VIII; R = 2-hydroxy-5-ethoxyphenyl for IX, X, XI, XII; R = 2-benzyloxy-5-methoxyphenyl for VIIa; R″ = benzyl ether of corresponding hydroxyphenyl compound; R′ = H for II, V, VI, IX, X; R′ = Me for III, IV, VII, VIII XI, XII.



2-hydroxyl group protected in form of an ester. The acetylation of 2-hydroxy-5-methoxypropiophenone yielded 2-acetoxy-5-methoxypropiophenone (XIIId) which was brominated in methanol (with de-esterification) to 2-hydroxy-5-methoxy-α-bromopropiophenone (XIIIc). Carbethoxylation of 2-hydroxy-5-methoxypropiophenone followed by nitrosation gave 2-ethylcarbonato-5-methoxy-α-isonitrosopropiophenone (XIVb). On hydrogenation it was found that the carbethoxyl was lost and this line of synthesis was abandoned.[3]

Since Compounds III, IV, VII, VIII, XI and XII were prepared by hydrogenation of ketones in weakly acidic solution, it is reasonable to assume that they possess the ephedrine rather than the pseudo ephedrine configuration.

Physiological Properties.—An extended report on the pharmacology of these substances will be published elsewhere. Briefly, the 2-hydroxy-5-methoxyphenylalkanolamines resemble rather closely their 2,5-dimethoxy analogs which are powerful, long-acting pressors, but are somewhat less potent and less toxic. Potency falls off in the other two classes, the 2,5-diethoxyphenylalkanolamines being the least active, and also the most toxic. Of the Compounds I–IV, only Compound III is at all comparable to the 2,5-dimethoxy series in length of action.

Experimental

Physical and analytical data on the substances isolated in pure form are presented in Table I. All melting points are corrected.

2-Hydroxy-5-alkoxyketones and 2,5-Diethoxyketones.—These compounds were prepared by Friedel–Crafts reactions between hydroquinone dialkyl ethers and the appropriate acyl chlorides or anhydrides. Since in these Friedel–Crafts reactions there is little tendency to form tarry or polymeric material, anhydrides were not superior to acyl chlorides for our purposes. In our hands some *o*-hydroxy ketone was always formed even under conditions designed to minimize dealkylation (addition of aluminum chloride to the other reactants below 5° and short reflux times). The amount of dealkylation could, however, be held below 20% under mild conditions. When more drastic conditions were employed (addition of acyl chloride last without temperature control and with longer reflux times) up to about 40% of 2-hydroxy-5-alkoxyketone could be obtained. With hydroquinone dimethyl ether the 2,5-dimethoxyketones were still isolated in 45–60% yield together with small amounts of starting material. With hydroquinone diethyl ether, dealkylation seemed to be easier and the more drastic conditions resulted in extensive formation of 2,5-dihydroxyketones which were not conveniently separated at this point. Mixtures of the 2-hydroxy-5-ethoxy and of 2,5-dihydroxyketones were usually benzylated, giving products easily separable by distillation.

TABLE I

Compound	M. p., °C.	Appearance[a]	Crystallizing solvent	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Intermediates in Synthesis of I					
Ic	94		Benzene–hexane	$C_{13}H_{18}O_5$	61.38	61.42	7.14	7.26
Ib	167		Absolute ethanol	$C_{13}H_{20}N_2O_4$	58.17	58.26	7.52	7.62
Ia	86.5	Small needles	Benzene–hexane	$C_{13}H_{17}NO_4$	62.12	62.42	6.82	6.79
			Ketones					
IIId	28[b]			$C_{13}H_{18}O_3$	70.23	70.18	8.17	7.77
Vd	50[c]	Stout prisms	Hexane	$C_{16}H_{16}O_3$	74.96	74.62	6.30	6.32
VIId	47[d]	Rhombs		$C_{17}H_{18}O_3$	75.52	75.36	6.72	7.04
XIIId	54	Rhombs	Hexane	$C_{12}H_{14}O_4$	64.83	64.67	6.35	6.40
IXd	42[e]	Needle-prisms	Hexane	$C_{17}H_{18}O_3$	75.51	75.79	6.72	6.80
XIe	82	Yellow needles	Hexane	$C_{11}H_{14}O_3$	68.00	68.31	7.27	7.40
XId	43[f]	Fine silky needles	Hexane	$C_{18}H_{20}O_3$	76.01	75.78	7.09	7.19
			α-Isonitrosoketones					
IIIb	84	Yellow powder	Ethyl acetate–hexane	$C_{13}H_{17}NO_4$	62.12	62.12	6.82	6.70
VIIb	98.5	Bright yel. need. prisms	Ethyl acetate–hexane	$C_{17}H_{17}NO_4$	68.20	68.25	5.73	6.01
XIVb	89–89.5	Golden yel. need. prisms	Ethyl acetate–hexane	$C_{13}H_{15}NO_6$	55.49	55.33	5.38	5.24
XIb	86	Yellow powder	Ethyl acetate–hexane	$C_{13}H_{19}NO_4$	68.97	68.82	6.11	6.49
			α-Bromoketones					
IIc	77	Leaflets	Methanol–hexane	$C_{12}H_{15}BrO_3$	50.17	50.49	5.27	5.41
IVc	42	Flat needles	Methanol–hexane	$C_{13}H_{17}BrO_3$	51.82	51.81	5.69	5.47
Vc	87–87.5	Needles	Ethyl acetate–hexane	$C_{16}H_{13}BrO_3$	57.31	57.22	4.51	5.01
XIIIc	60	Yellow powder	Hexane	$C_{10}H_{11}BrO_3$	46.33	46.15	4.28	4.35
VIIIc	60	Prisms	Hexane	$C_{17}H_{17}BrO_3$	58.44	58.69	4.99	4.93
IXc	73	Platelets	Hexane	$C_{17}H_{17}BrO_3$	58.44	58.72	4.99	4.76
XIIc	78		Hexane	$C_{18}H_{19}BrO_3$	59.49	59.26	5.28	5.55
			α-Aminoketone hydrochlorides					
IIIa	161		Abs. ethanol–ether	$C_{13}H_{20}ClNO_3$	57.01	56.81	7.37	7.29
Va	192–193	Yellow rhombs	Aqueous alcohol	$C_9H_{12}ClNO_3$	49.64	49.52	5.56	5.79
VIIa	179.5	Felted needles	Absolute ethanol	$C_{17}H_{19}ClNO_3$	63.43	63.58	6.27	6.31
IXa	182–185 (dec.)	Pale yellow needles	Abs. ethanol–ether	$C_{10}H_{14}ClNO_3$	51.82	51.64	6.10	6.00
			α-Methylaminoketone hydrochlorides					
IIa	163	Fine felted needles	Absolute ethanol	$C_{13}H_{20}ClNO_3$	57.01	57.05	7.37	7.63
Xa	186	Small stout prisms	Absolute ethanol	$C_{11}H_{16}ClNO_3$	53.75	53.94	6.57	6.62
XIIa	164.5	Yellow leaflets	Absolute ethanol	$C_{12}H_{18}ClNO_3$	55.47	55.60	6.99	6.86
			Tertiary aminoketone hydrochlorides					
IIb	145		Abs. ethanol–ether	$C_{20}H_{26}ClNO_3$	65.99	65.74	6.93	6.93
VIb	156.5–158	Hexagonal prisms	Abs. ethanol–ether	$C_{24}H_{26}ClNO_3$	69.96	69.82	6.37	6.55
IXb	185–187 (dec.)	Silky needles	Abs. ethanol–ether	$C_{31}H_{32}ClNO_3$	74.15	73.99	6.43	6.43
			Aminoalcohol hydrochlorides					
I	178		Abs. ethanol–ether	$C_{12}H_{20}ClNO_3$	55.04	55.12	7.71	7.68
II	150		Abs. ethanol	$C_{13}H_{22}ClNO_3$	56.59	56.60	8.04	7.88
III	216	Fine needles	Abs. ethanol	$C_{13}H_{22}ClNO_3$	56.59	56.28	8.04	7.91
IV	146		Abs. ethanol–ether	$C_{14}H_{24}ClNO_3$	58.00	57.69	8.35	8.10
V	160	Leaflets	Abs. ethanol–ether	$C_9H_{14}ClNO_3$	49.19	49.43	6.43	6.53
VI	130	Rhombs	Abs. ethanol–ether	$C_{10}H_{16}ClNO_3$	51.37	51.57	6.91	7.11
VII	228 (dec.)	Prisms	Abs. ethanol	$C_{10}H_{15}ClNO_3$	51.37	51.67	6.91	7.06
VIII	202		Abs. ethanol	$C_{11}H_{18}ClNO_3$	53.31	53.21	7.33	7.59
IX	152.5–153	Platelets	Abs. ethanol–ether	$C_{10}H_{16}ClNO_3$	51.37	51.43	6.91	6.66
X	133		Abs. ethanol–ether	$C_{11}H_{18}ClNO_3$	53.31	53.13	7.33	7.51
XI	217 (dec.)		Abs. ethanol	$C_{11}H_{18}ClNO_3$	53.31	53.09	7.33	7.38
XII	182.5	Fine felted needles	Abs. ethanol–ether	$C_{12}H_{20}ClNO_3$	55.04	54.93	7.71	7.52

[a] Appearance noted only when characteristic. [b] B. p. (18 mm.) 178–180°. [c] B. p. (1 mm.) 187–192°. [d] B. p. (1 mm.) 194–196°. [e] B. p. (1 mm.) 198–202°. [f] B. p. (1 mm.) 198–202°.

2-Benzyloxy-5-alkoxyketones.—The crude alkali-soluble fractions from Friedel–Crafts reactions were benzylated in methanol with potassium hydroxide and benzyl chloride, slightly less than one equivalent of each being added initially with two later additions of half equivalents at two-hour intervals. Stirring was found to be desirable in order to minimize bumping. The products were washed with alkali, dried over potassium carbonate and distilled *in vacuo*. Yields varied from 60–90% dependent largely on the amount of dihydroxyketone present.

α-Bromoketones.—Bromination was carried out in methanol solution as described in Paper III of this series.[8] Yields of pure product varied between 55 and 90%, the lower yields corresponding to the lower-melting and more soluble compounds.

α-Isonitrosopropiophenones.—The propiophenones were nitrosated by the methyl nitrite method of Hartung and Crossley.[7] Yields were from 50–75% of pure isonitrosoketone.

Tertiary Aminoketones.—The technique used in the reaction of benzylmethylamine with the α-bromoketones was that of Ardis, Baltzly and Schoen.[3] It became apparent during the course of this work that the acetic anhydride treatment was not adequate to remove traces of secondary amine from the tertiary aminoketones and, due largely to this defect, only two of the six α-benzylmethylamines were obtained analytically pure. One of these, IIb, was isolated in an 89% yield, the other (VIb) in only 20%. The quantities of benzylmethylamine hydrobromide precipitated from the reaction mixture were in all cases approximately the calculated amount and it is believed that the reaction itself is effectively quantitative. Of the four tertiary aminoketones that had to be reduced as crude preparations, two afforded pure α-methylaminoketones (Xa and XIIa) after debenzylation. The yields of Xa and XIIa were 90 and 55%, respectively, reckoned on the crude tertiary aminoketones employed. In the other two lines of synthesis, only the final aminoalcohols (IV and VIII) were completely pure—the intermediates were crystalline but apparently contaminated with tenacious impurities.

Compound IXb (2-benzyloxy-5-ethoxy-α-dibenzylaminoacetophenone) was prepared by treating 0.05 mole of the corresponding bromoketone (IXc) with 0.1 mole of dibenzylamine in 500 cc. of absolute ether at room temperature. After standing 40 hours, 7 g. (0.025 mole) of dibenzylamine hydrobromide was obtained. Only 3 g. more separated after standing three days longer. The filtrate from the salt was extracted with water, allowed to stand three hours with 5 cc. of acetic anhydride and then shaken with 1 *N* hydrochloric acid solution. At this point, a copious precipitate formed and was filtered off. After recrystallization of this solid, analysis showed it to be the desired product (IXb). The yield was 60%. The technique of Simonoff and Hartung[6] might have given better results but seemed inadvisable at the time.

α-Methylaminoketones.—The palladized charcoal reduction of the α-benzylmethylaminoketone hydrochlorides removed the N-benzyl groups smoothly and the 2-benzyl group when present. Compounds IIa, Xa and XIIa were isolated in good yield. The product of the reduction of VIb was hydrogenated directly with platinum without attempting the isolation of the intermediate. The precursors of IV and VIII, although crystalline, could not be purified so as to give satisfactory analyses. When debenzylation can be applied to a pure substance the reaction is usually quantitative. The reduction of IIb, for example, gave the calculated quantity of IIa, and after two recrystallizations the yield was 75%.

α-Aminoketones.—Compound Va was prepared by the hexamethylenetetramine method. The initial product of the hydrolysis with alcoholic hydrogen chloride of the addition compound from hexamethylenetetramine and Vc was not readily separated from ammonium chloride. The crude product, contaminated with ammonium chloride, was debenzylated with palladized charcoal yielding Va which was purified easily. The yield was 55% from the bromoketone Vc. A similar situation had been found with the 5-methyl analog.[3] The debenzylation of IXb afforded IXa in quantitative yield.

The aminopropiophenones IIIa and VIIa were prepared by reduction of the corresponding isonitroso ketones with palladized charcoal in alcoholic hydrogen chloride solution. Yields were 60–70% of pure material. The reduction of XIb to XI was performed in two stages with no attempt to isolate the intermediate aminoketone.

Aminoalcohols.—With the exception of Compound I, all the aminoalcohols were prepared by hydrogenation of the corresponding aminoketone hydrochlorides with platinum catalyst. Yields of pure compounds were 40 to 90% dependent largely on losses in crystallization.

Compound I was prepared by the line of synthesis indicated in Chart I and followed by Baltzly and Buck,[2] in the preparation of the 2,5-dimethoxy analog. The substances shown in Chart I are those actually isolated. The 2,5-diethoxybenzaldehyde was prepared in 57% yield by the Gattermann reaction. The product from the Reformatzky reaction of this aldehyde and ethyl bromoacetate was saponified in the cold and the β-hydroxy acid Ic (yield 72%) was purified by recrystallization. Reesterification was accomplished by the use of diazomethane (to avoid dehydration) and the ester was refluxed directly with alcoholic hydrazine hydrate forming Ib, in effect quantitatively. The azide obtained from Ib by the action of cold nitrous acid was taken up in benzene and dried briefly. Cautious warming of the benzene solution of the azide produced the oxazolidone Ia in 67% yield from the hydrazide. Cleavage with cold concentrated hydrochloric acid[8] afforded I, yield 50% after two crystallizations.

Acknowledgment.—The authors wish to express their gratitude to Mr. Samuel W. Blackman for the microanalyses here reported.

Summary

The primary and secondary aminoalcohols of the 2,5-diethoxy, 2-hydroxy-5-methoxy and 2-hydroxy-5-ethoxyphenethyl and phenylisopropylamine series have been prepared.

TUCKAHOE 7, NEW YORK RECEIVED APRIL 10, 1947

(7) Hartung and Crossley, "Organic Syntheses," **16**, 45 (1936).

(8) *Cf.* Schroeter, German Patent, 220,852.