one-half hours with acetic acid (5 cc.), sulfuric acid (5 cc.) and water (5 cc.). The red solution was poured over ice and the brown solid was removed by ether extraction. The ether layer was extracted twice with sodium carbonate solution (10%, 35 cc. each time). The carbonate extract was warmed to expel ether, then cooled and acidified. The solid was removed and crystallized from ether–petroleum ether (b. p. 60–68°), followed by crystallization from petroleum ether alone. The acid XX (0.77 g., 44%) formed colorless needles which melted at 120–121°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.54; H, 7.30.

2,5-Dimethoxy-3,4-dimethyl-6-bromophenylacetic Acid (XIII).—A. The acid XX (0.25 g.) in chloroform (10 cc.) was brominated by addition of a solution of bromine (0.2 g.) in chloroform (3 cc.). The solution was stirred at room temperature overnight. The solvent was evaporated and the residue was washed with a little cold benzene and then recrystallized from benzene–petroleum ether (b. p. 60–68°). The acid melted at 151–153.5°. B. The methoxyisocoumaranone XIV (0.26 g.) was dissolved in methanol (4 cc.) containing methyl sulfate (4 cc.). The solution was refluxed while a solution of potassium hydroxide (4 g.) in methanol (20 cc.) was added. The mixture was refluxed for an hour and was then diluted with water and acidified with hydrochloric acid. The solution, on standing in the refrigerator overnight, deposited 0.16 g. (57%) of the phenylacetic acid XIII which melted at 151–154°. C. The isocoumaranone VIII (1.1 g.) in methanol (15 cc.) was treated with potassium hydroxide (13 g.) in methanol (65 cc.) as described under B. The alkaline solution was diluted with water, extracted once with ether, and then warmed to expel ether. The cooled solution was acidified and the precipitate was removed and crystallized once from dilute methanol and twice from benzene–petroleum ether (b. p. 60–68°). The pure acid XIII (0.81 g., 63%) formed white needles which melted at 154–155°. The products from A, B, and C were identical, as shown by mixed melting point determination. Large depressions in the melting point resulted when the acid was mixed with VIII (m. p. 155–156°) or with XVI (m. p. 141–143°).

Anal. Calcd. for $C_{12}H_{15}O_4Br$: C, 47.52; H, 4.95. Found: (sample from C) C, 47.68; H, 4.99.

Summary

1. Dibromo-*o*-xyloquinone and sodium malonic ester react in cold dioxane to give a substitution product, 3-bromo-2-dicarbethoxymethyl-5,6-dimethylbenzoquinone (III). If the reaction time is prolonged, both bromine atoms of the quinone are replaced by malonic ester groups.

2. The reaction is confined entirely to the bromine atoms. No trace was found of a coumarin formed by attack of the reagent upon a methyl group of the quinone. This behavior of the quinone is in contrast with that of the isomeric dibromo-*m*-xyloquinone, in which the bromine atoms are inert and the only attack by sodium malonic ester is at a methyl group.

3. Many derivatives of the hydroquinone-malonic ester V have been prepared, and the substances obtained from it by ring closure have been studied.

4. One of the degradation products of V, namely, 2,5-dimethoxy-3,4-dimethyl-6-bromophenylacetic acid (XIII) was synthesized by an independent method starting with *o*-xylohydroquinone.

5. Improved procedures are given for preparation of *o*-xyloquinone and some of its derivatives.

MINNEAPOLIS, MINNESOTA RECEIVED DECEMBER 1, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

α,β-Dialkylphenethylamines. Alkylation of Phenylacetone

BY C. M. SUTER AND ARTHUR W. WESTON[1]

Although numerous substituted phenethylamines have been prepared since the discovery of the physiological activity associated with the $C_6H_5C—C—N$ structure, compounds having alkyl groups attached to both the *alpha* and *beta* carbons have not been reported. In the present investigation several amines with the general formula $C_6H_5CHRCHNH_2CH_3$, one such compound with a methyl on the nitrogen, and also one amine with two alkyls on the beta carbon, $C_6H_5C(CH_3)_2CHNH_2CH_3$, have been synthesized from the corresponding ketones and some data on their physiological action have been obtained.

A number of alkylations of phenylacetone and similar ketones in the presence of sodium ethoxide have been described by Tiffeneau and co-workers.[2] In the present work it was found that the reaction of methyl iodide with phenylacetone in the presence of one equivalent of sodium ethoxide gave a mixture in which unreacted phenylacetone predominated. It seemed probable that this re-

(1) Sharp and Dohme Research Associate, 1938–1940.

(2) Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **33**, 759 (1923); Lévy and Jullien, *ibid.*, **45**, 941 (1929).

sult could be ascribed to the low acidity of the methylene hydrogen in the ketone which favored the reaction going to the left.

$$C_2H_5O^- + C_6H_5CH_2COCH_3 \rightleftharpoons C_2H_5OH + [C_6H_5CHCOCH_3]^-$$

When the alkylation was effected in the presence of sodium isopropoxide the yield of methylated ketone was good. The introduction of a second methyl group did not occur readily even under these conditions but took place easily in the presence of potassium *t*-butoxide. On the basis of these results the alcohols and ketones may be arranged in a series in the order of decreasing acidity.

$$C_2H_5OH > C_6H_5CH_2COCH_3 > CH_3CHOHCH_3 > C_6H_5CH(CH_3)COCH_3 > (CH_3)_3COH$$

Cope and Hancock[3] reported that isopropyl alcohol is a better solvent than ethyl alcohol for the alkylation of alkylidenecyanoacetic esters, but here the advantage was credited to the relative effectiveness of the alcohols in bringing about alcoholysis.

In the action of formamide upon the alkylphenylacetones both racemic amines were formed. The alkaline hydrolysis of the intermediate amides, $C_6H_5CHRCH(NHOCH)CH_3$, gave a progressively smaller yield of amine as the alkyl became larger. The low yield was caused by the inertness of the amide to alkali rather than lack of reaction between formamide and the ketone since hydrolysis of the reaction mixtures with acid gave good yields of the amines.

It is conceivable that in the reaction of formamide with dimethylphenylacetone, $C_6H_5C(CH_3)_2COCH_3$, rearrangement might occur, but since only one amine was obtained and this was not the most likely rearrangement product,[4] $C_6H_5C(CH_3)(NH_2)CH(CH_3)_2$, it is evident that the desired compound, $C_6H_5C(CH_3)_2CHNH_2CH_3$, was actually formed. This is in accord with the physiological activity of the amine.

The reaction of methylformamide[5] with α-methylphenylacetone occurred slowly. After twelve hours much of the ketone remained unchanged, and even after long heating the yield of pure amine recovered was only about 16% of the theoretical amount. The hydrochloride was apparently a mixture of the two racemates, but they were not separated.

(3) Cope and Hancock, THIS JOURNAL, **60**, 2903 (1938).

(4) Konowalow and Jegorow, *J. Russ. Phys.-Chem. Soc.*, **30**, 1033 (1898).

(5) Novelli, THIS JOURNAL, **61**, 520 (1939).

Experiments on the physiological action of the phenethyl amines on white mice[6] demonstrated that the substitution of one alkyl group in the beta position greatly reduces the toxicity. The compound with two beta methyl groups is slightly more toxic than that having only one. The toxicity apparently increases slightly with the size of the alkyl group. In Table I are listed the results obtained with the amines prepared in the present investigation; for comparison, data on two known amines are included. They were all tested as their hydrochlorides. The (I) and (II) after the formulas for the amines in the first column indicate the low- and high-melting hydrochlorides, respectively, corresponding to the two racemates.

In blood pressure tests, all the compounds of Table I showed about the same depressor activity in the rabbit. In dogs the pressor activities

TABLE I

TOXICITY OF AMINE HYDROCHLORIDES IN MG./KG.

Amine	Toxicity LD 0	LD 50	LD 100	No. of animals
$C_6H_5CH_2CHNH_2CH_3$	15	45	80	65
$C_6H_5CH(CH_3)CHNH_2CH_3$	200	290	400	30
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (I)	100	180	350	40
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (II)	200	250	350	30
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (I)	100	180	225	40
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (II)	100	140	160	40
$C_6H_5C(CH_3)_2CHNH_2CH_3$	100	160	225	45
$C_6H_5CH_2CH(NHCH_3)CH_3$	100	150	225	..
$C_6H_5CH(CH_3)CH(NHCH_3)CH_3$	100	165	225	..

of α-methylphenethylamine and of α,β-dimethylphenethylamine were similar and greater than for the other compounds. All compounds produced a greater rise of diastolic pressure than of systolic pressure. Some of the compounds possess analeptic activity and this is under further investigation.

Experimental

Preparation of Alkylphenylacetones.—Alkylation[2] of 13.4 g. (0.1 mole) of phenylacetone in 25 ml. of absolute alcohol, to which 2.3 g. (0.1 mole) of sodium had been added, with 20 g. (0.14 mole) of methyl iodide gave upon distillation 5.8 g. of a mixture of phenylacetone and methylphenylacetone in which the former predominated. There remained about 10 ml. of a viscous liquid which did not distill at 250° (15 mm.).

Alkylation of 10.7 g. (0.08 mole) of phenylacetone in 60 ml. of dry isopropyl alcohol, in which 1.84 g. (0.08 mole) of sodium had been dissolved, with 11.5 g. (0.088 mole) of methyl iodide gave 8.75 g. (74% yield) of ketone, b. p. 103–106° (22 mm.). An experiment exactly the same as

(6) We are greatly indebted to Dr. Paul A. Mattis and Mr. Albert R. Latven of the Medical Research Division, Sharp and Dohme for a report of their experiments. The tests were made according to the procedure outlined in a previous paper [Suter and Weston, *ibid.*, **63**, 602 (1941)].

TABLE II

PROPERTIES OF ALKYLPHENYLACETONES

Ketone	Yield, %	B. p., °C. (p., mm.)	$n^{20}D$	d^{20}_4	M_D Calcd.	M_D Found
$C_6H_5CH(CH_3)COCH_3$[a,b,d]	74	106–107(22)	1.5092	0.9816	44.79	45.03
$C_6H_5CH(C_2H_5)COCH_3$[b]	55	110(18)	1.5051	.9681	49.41	49.69
$C_6H_5CH(C_3H_7\text{-}n)COCH_3$[c]	55	114–115(13)	1.5020	.9556	54.03	54.34
$C_6H_5C(CH_3)_2COCH_3$[d]	50	99- 99.5 (12)	1.5083	.9748	49.41	49.82

[a] Darzens, *Compt. rend.*, **141**, 767 (1905); Favorskiĭ and Chilingaren, *ibid.*, **182**, 221 (1926); Van Zoeren, U. S. Pat. 2,225,671, *C. A.* **35**, 2156 (1941). [b] Tiffeneau, *Compt. rend.*, **143**, 650 (1906); *Ann. chim. phys.*, [8] **10**, 362 (1907). [c] Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **33**, 759 (1923); *Compt. rend.*, **176**, 312 (1923); Lévy and Jullien, *Bull. soc. chim.*, [4] **45**, 941 (1929); Tiffeneau, Lévy and Jullien, *ibid.*, [4] **49**, 1788 (1931). [d] Favorskiĭ, Zalesskaya, Rozanov and Chelintzev, *ibid.*, [5] **3**, 239 (1936); *J. Gen. Chem.* (U. S. S. R.), **5**, 1728 (1935); Ramart-Lucas and Bruzau, *Bull. soc. chim.*, [5] **1**, 119 (1934).

the above, except that methyl sulfate was substituted for the methyl iodide, gave an unsatisfactory product.

The alkylation of phenylacetone with ethyl iodide and *n*-propyl iodide was carried out exactly as with the methyl compound. The introduction of the second methyl group into phenylacetone was effected by the following procedure.

A solution of potassium *t*-butoxide was prepared by dissolving 5.2 g. (0.13 mole) of potassium metal in a mixture of 45 ml. of pure *t*-butyl alcohol and 6 ml. of dry toluene. There were then added 19.4 g. (0.13 mole) of methyl α-phenylethyl ketone and gradually 25 g. (0.176 mole) of methyl iodide. Reaction occurred immediately and was complete at the end of the addition of the methyl iodide. The alcohol was removed on the steam-bath, water was added to the residue to dissolve the sodium iodide and the water insoluble layer removed. Two ether extracts of the water layer were combined with this, and the oil remaining after removal of the ether was fractionated through an efficient column. This gave 10.7 g. of an oil distilling at 99–102° (12 mm.). This was a 50% yield.

All of the ketones prepared have been described in the literature previously but their refractive indices have not been reported. In Table II are given data for the ketones prepared by the alkylation procedures just described and references to previous methods of preparation.

The identity of each ketone was checked by preparation of its semicarbazone. These had melting points in satisfactory agreement with those given in the literature[7] except for the *n*-propyl compound. It seemed of interest to determine whether semicarbazones derived from benzyl ketones containing one active hydrogen could be analyzed by a recent modification of the Jamieson[8] method. The results in Table III indicate that no appreciable excess of potassium iodate was consumed in the titration of the ethyl and *n*-propyl compounds.

TABLE III

Semicarbazone of	M. p., °C.	Anal., eq. wt. Calcd.	Found
$C_6H_5CH(C_2H_5)COCH_3$	190.5–191.5	54.82	54.73
$C_6H_5CH(C_3H_7\text{-}n)COCH_3$	137 –137.5	58.32	58.22
$C_6H_5C(CH_3)_2COCH_3$	185.5–186.5	54.82	54.92

Preparation of α,β-Dialkylphenethylamines.—The procedure used was adapted from that of Johns and Burch.[9] The preparation of the α-methyl-β-ethylphenethylamine will be described. A mixture of 10.2 g. (0.063 mole) of methyl α-phenyl-*n*-propyl ketone and 15 g. (0.334 mole) of formamide was heated to vigorous bubbling under an air condenser for seventeen hours. About 33 ml. of 30% sodium hydroxide was added and the mixture refluxed for sixteen hours. It was then extracted three times with ether, the ether solution washed three times with 10% hydrochloric acid and dried over sodium sulfate. The acid solution was made alkaline and extracted with ether. After drying over potassium carbonate and distilling there was obtained 2.88 g. or 28% of the theoretical amount of amine. From the ether solution containing acid insoluble material was obtained a viscous oil which (after refluxing with 8 ml. of concentrated hydrochloric acid for twenty-four hours, making alkaline and extracting as above) gave after distillation 4.96 g. of amine, b. p. 108–110.5° (19

TABLE IV

PREPARATION OF AMINES

Amine	Yield, %	B. p., °C. (p., mm.)	Anal., n. eq. Calcd.	Found
$C_6H_5CH(CH_3)CHNH_2CH_3$	60[b]	118–119 (19)	149.2	150.6
$C_6H_5CH(C_2H_5)CHNH_2CH_3$	63	118 (19)	163.2	161.2, 161.5
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$[a]	68.5	116(15)	177.2	175, 175
$C_6H_5C(CH_3)_2CHNH_2CH_3$	76.5[c]	105–106 (13)	163.2	161
$C_6H_5CH(CH_3)CH(NHCH_3)CH_3$	16[c,d]	111(24)	163.2	163.6

[a] The formyl derivative was isolated before acid hydrolysis, b. p. 162.5–164° (6 mm.). [b] Alkaline hydrolysis only. [c] Acid hydrolysis only. [d] The yield of $C_6H_5CH_2CH(NHCH_3)CH_3$ was 22% by this method.

TABLE V

PROPERTIES OF AMINES

Amine	$n^{20}D$	d^{20}_4	M_D Calcd.	Found
$C_6H_5CH(CH_3)CHNH_2CH_3$	1.5180	0.9374	48.20	48.19
$C_6H_5CH(C_2H_5)CHNH_2CH_3$	1.5126	.9272	52.82	52.87
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$	1.5084	.9172	57.44	57.66
$C_6H_5C(CH_3)_2CHNH_2CH_3$	1.5212	.9430	52.82	52.71
$C_6H_5CH(CH_3)CH(NHCH_3)CH_3$	1.5091	.9236	52.99	52.77

(7) See references of Table II.

(8) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

(9) Johns and Burch, THIS JOURNAL, **60**, 919 (1938).

TABLE VI

Hydrochloride of	M. p., °C.	Solvent	Anal., Cl, % Calcd.	Found
$C_6H_5CH(CH_3)CHNH_2CH_3$	136 -139	$C_6H_5CH_3$	19.12	19.25
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (I)	171 -172	$CHCl_3$[a]	17.78	17.89
$C_6H_5CH(C_2H_5)CHNH_2CH_3$ (II)	258 -261	$CHCl_3 + C_6H_{14}$[b]	17.78	17.80
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (I)	120 -123	C_6H_6	16.61	16.48
$C_6H_5CH(C_3H_7\text{-}n)CHNH_2CH_3$ (II)	250 -253	$(C_2H_5)_2O$[c]	16.61	16.81
$C_6H_5C(CH_3)_2CHNH_2CH_3$	213.5-215	$(CH_3)_2CO$	17.78	17.91
$C_6H_5CH(CH_3)CH(NHCH_3)CH_3$	116 -120	$CH_3CO_2C_2H_5$	17.78	17.78

[a] Dry acetone is also suitable. [b] Very soluble in chloroform, precipitated by petroleum ether. [c] Less soluble than low melting isomer. Further crystallization was from benzene and petroleum ether.

mm.). The total yield from acid and alkaline hydrolyses was 6.45 g. or 63% of the theoretical amount.

In the alkaline hydrolysis of the product from the action of formamide upon methyl α-phenyl-*n*-butyl ketone the yield of amine was only 5.3% while from subsequent acid hydrolysis the amine obtained amounted to an 86% yield, based upon the formyl derivative used.

In the preparation of N, α,β-trimethylphenethylamine methylformamide[5] was substituted for formamide. In Tables IV and V the data for the amines are summarized. They were obtained as clear viscous liquids which were mixtures of diastereoisomers (except for the compound from the dimethyl ketone).

Amine Hydrochlorides.—The five amines were converted into their hydrochlorides by dissolving in ether and passing in dry hydrogen chloride. Fractional crystallization of the precipitates yielded the diastereoisomers in the case of the β-ethyl and β-*n*-propylamines. There was evidence of the existence of two compounds in the case of the methyl homolog but only one was obtained pure. α,β,β-Trimethylphenethylamine gave only one hydrochloride in conformity with the assigned structure. The data for the hydrochlorides are summarized in Table VI.

Summary

1. The monomethylation of phenylacetone is incomplete in the presence of sodium ethoxide in ethyl alcohol but proceeds readily with sodium isopropoxide in isopropyl alcohol. To introduce the second methyl group potassium *t*-butoxide is required.

2. A series of α-methyl-β-alkylphenethylamines has been prepared by the action of formamide upon the corresponding ketones. In two instances both diastereoisomeric forms of the amine hydrochlorides have been isolated by fractional crystallization.

3. The substitution of an alkyl group on the β-carbon of α-methylphenethylamine greatly reduces its toxic properties without a corresponding loss in pressor activity.

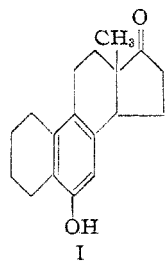
EVANSTON, ILLINOIS RECEIVED DECEMBER 2, 1941

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN

The Synthesis of an Isomer of Estrone Containing a Phenolic B Ring

BY W. E. BACHMANN AND A. B. NESS[1]

In continuation of our work on the synthesis of sex hormones and related compounds,[2] we have prepared 6-hydroxy-1,2,3,4-tetrahydro-17-equilenone (I), an isomer of estrone in which the B ring rather than the A ring is phenolic. We were interested in determining what effect this change in structure would have on the estrogenic activity of the molecule.



I

For the synthesis of this compound, the methyl ether of 5,6,7,8-tetrahydro-1-naphthol was condensed with succinic anhydride and the resulting keto acid was reduced by the Clemmensen method to II. The structure of the product was established by its conversion to the known γ-4-methoxy-1-naphthylbutyric acid by catalytic dehydrogenation of its methyl ester and hydrolysis of the product. Cyclization of the acid chloride of II yielded 1-keto-9-methoxy-*s*-octahydrophenanthrene (III), whose structure was established

(1) From the Ph.D. dissertation of A. B. Ness.

(2) Previous paper in this series, Bachmann and Thomas, THIS JOURNAL, **64**, 94 (1942).