[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Compounds Containing the Pyrrolidine Ring. Analogs of Sympathomimetic Amines

BY R. V. HEINZELMAN AND B. D. ASPERGREN

RECEIVED JANUARY 28, 1953

Twenty-six phenylalkyl pyrrolidines have been prepared in which a variety of substituents have been placed in the benzene ring, in the alkyl side chain and in the pyrrolidine ring. Several of these compounds have been found to possess considerable bronchodilator activity. The Voigt reaction has been extended to heterocyclic secondary amines and the mechanism of this reaction is discussed briefly.

The classical studies of many workers on the so-called pressor amines and more recent investigations[1] in these laboratories have been aimed in part at an attempt to bring into this field an understanding of the effect of substitution in the various positions of the phenethylamine skeleton on the kind of activity obtained. Among the many types of substitution studied may be mentioned hydroxyl, alkoxyl, alkyl, amino and halogen groups in the aromatic ring; alkyl, hydroxyl, alkoxyl, aroyloxyl and amino groups on the beta carbon atom; alkyl, aryl, hydroxyl and alkoxyl groups on the alpha carbon atom; and alkyl, cycloalkyl and aralkyl groups on the amino nitrogen atom. Of all these variations, perhaps the least studied is the effect of the presence of a tertiary nitrogen on the physiological activity and more especially on the bronchodilator activity of such compounds.

Studies carried out in our laboratories,[1i] as well as a number of reports and patents[2] appearing in the literature, indicate interesting pharmacological activity among tertiary amines of the phenethylamine series. As part of a study of pyrrolidine compounds we have prepared a number of pyrrolidine analogs of phenethylamines and similar compounds, having a variety of substituents on the alpha and beta carbon atoms and in the aromatic ring.

The compounds prepared in this work are indicated in Table I.

The members of the series in which R is H (Table I) were prepared by condensing the appropriately substituted phenylacetone or desoxybenzoin with a pyrrolidine in the absence (method B) or presence (method C) of calcium oxide and simultaneous or subsequent hydrogenation with Adams platinum oxide as the catalyst.

When phenylacetone or ring-substituted phenylacetone derivatives were employed, method B was always quite satisfactory, although an intermediate Schiff base cannot be postulated in this reaction. When desoxybenzoins were used, it was necessary to resort to method C. In the case of *p*-desoxyanisoin neither procedure proved successful; the nitrogen-free hydrogenation product from B probably represented reduced ketone, while in C only a small amount of hydrogen was absorbed. Since an excess of pyrrolidine was used with method C in every case, it was impossible to decide whether this reaction proceeded through the type of intermediate postulated by Mannich and Davidsen[3] (*i.e.*, a β-dipyrrolidyl-α,β-diarylethane which splits off pyrrolidine prior to hydrogenation or through a pyrrolidyl stilbene structure formed directly by condensation with one equivalent of base with the loss of a mole of water).

The methods used in attempting to prepare the series in which R is OH are indicated in Fig. 1.

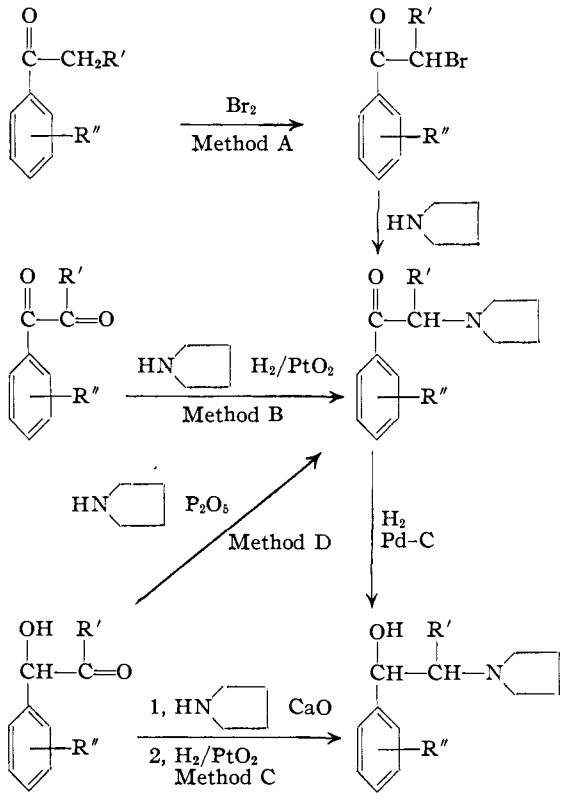


Fig. 1.

Method A[4] alone was used when R′ was H. As

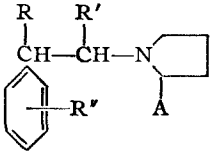
(1) For example: (a) F. R. Curtis, *J. Pharmacol.*, **35**, 321 (1929); (b) M. L. Tainter, J. R. Pedden and M. James, *ibid.*, **51**, 371 (1934); (c) H. Handovsky, *Arch. intern. Pharmacodynamie*, **51**, 301 (1935); (d) H. Konzett, *Arch. exptl. Path. Pharmacol.*, **197**, 27, 41 (1940); (e) B. E. Graham, G. F. Cartland and E. H. Woodruff, *Ind. Eng. Chem.*, **37**, 149 (1945); (f) J. R. Corrigan, M. Langerman and M. L. Moore, THIS JOURNAL, **67**, 1894 (1945); (g) A. M. Lands and co-workers, *J. Pharmacol.*, **89**, 297 (1947); *ibid.*, **90**, 110, 254 (1947); (h) R. V. Heinzelman, THIS JOURNAL, **75**, 921 (1953); (i) R. V. Heinzelman and B. D. Aspergren, THIS JOURNAL, **75**, 925 (1953).

(2) P. B. Report 32536, Ser. 459 VA; H. Handovsky, *Arch. intern. Pharmacodynamie*, **51**, 301 (1935); U. S. Patents, 1,399,312; 2,088,941; 2,234,933; British Patent 431,848; German Patents 611,501; 615,412; 697,805; 699,249; 699,250.

(3) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936). In our work, using method C, it was always found necessary to heat the mixture for some time prior to the catalytic hydrogenation.

(4) N. Rubin and A. R. Day, *J. Org. Chem.*, **5**, 54 (1940); R. Baltzly and J. S. Buck, THIS JOURNAL, **62**, 164 (1940); J. R. Corrigan, M. Langerman and M. L. Moore, *ibid.*, **67**, 1894 (1945); R. Siminoff and W. H. Hartung, *J. Am. Pharm. Assoc., Sci. Ed.*, **35**, 306 (1946); A. E. Ardis, R. Baltzly and W. Schoen, THIS JOURNAL, **68**, 591 (1946); British Patent 297,756; German Patent 638,650.

TABLE I

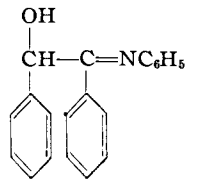


No.	R	R′	R″	A	Method used	B.p. °C.	Mm.	M.p., °C. HCl[a]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
1	H	CH_3	H	H	B			162.5–163(T)	$C_{13}H_{20}ClN$	69.16	69.00	8.93	8.78			6.20	6.30
2	H	CH_3	*o*-OCH_3	H	B	118[b]	0.5	152–153(T)	$C_{14}H_{22}ClNO$	65.73	65.85	8.67	8.67			5.48	5.49
						155–160	14										
3	H	CH_3	*p*-OCH_3	H	B	120	0.6	144–145(T)	$C_{14}H_{22}ClNO$	65.73	65.80	8.67	8.47			5.48	5.50
4	H	CH_3	*o*-OCH_3	CH_3	B	156–159[c]	12	155.7–156.5	$C_{15}H_{24}ClNO$	66.77	66.84	9.07	9.12	13.14	13.16	5.19	5.16
5	H	CH_3	H	C_6H_5	B	148–152[d]	1.0	152.5–159(T)[e]	$C_{19}H_{24}ClNO$	75.60	75.51	8.01	7.97	11.75	11.76	4.64	4.99
6	H	CH_3	*o*-OCH_3	C_6H_5	B	180–185[f]	1.0	194–200(T)[e]	$C_{20}H_{26}ClNO$	72.37	72.57	7.90	7.91	10.68	10.76	4.22	4.22
7	H	CH_3	*p*-OCH_3	C_6H_5	B	183–185[g]	0.8	153.5–158(T)[e,h]	$C_{26}H_{28}N_4O_8$[h]	59.53[h]	59.74	5.38	5.45			10.68	10.08
8	H	C_6H_5	H	H	C	125–127	0.8	212(B)	$C_{18}H_{22}ClN$	75.11	75.10	7.71	7.69			4.87	5.23
9	H	*p*-$C_6H_4OCH_3$	*p*-OCH_3	H	[i]												
10	=O[j]	H	*m*-OCH_3	H	A			158–160(T)	$C_{13}H_{18}ClNO_2$	61.05	60.82	7.09	7.07	13.82	13.63	5.48	5.34
11	OH	H	*m*-OCH_3	H				133–135(B)	$C_{13}H_{20}ClNO_2$	60.57	60.41	7.82	7.60	13.76	13.45	5.44	5.42
12	OH	H	*p*-OCH_3	H	A[k]			176–178(B)	$C_{13}H_{20}ClNO_2$	60.57	59.46	7.82	7.80	13.76	13.58	5.44	5.51
13	=O	H	3,4-diOH	H	A			244(B, dec.)	$C_{12}H_{16}ClNO_3$	55.92	55.95	6.26	6.16			5.44	5.60
14	OH	H	3,4-diOH	H				168–169(B)	$C_{12}H_{18}ClNO_3$	55.49	55.63	6.98	6.72	13.65	13.60	5.39	5.55
15	=O	CH_3	H	H	A[l]			197(B)	$C_{13}H_{18}ClNO$	65.13	64.59	7.40	7.48	14.79	14.73	5.84	5.83
16	OH	CH_3	H	H				210–212(B)	$C_{13}H_{20}ClNO$	64.58	64.00	8.34	8.07	14.67	14.56	5.79	5.86
								126–128(B)[m]	$C_{19}H_{22}N_4O_8$[m]	52.53[m]	52.47	5.11	5.02			12.90	12.71
17	=O	CH_3	*o*-OCH_3	H	A			162–163(B)	$C_{14}H_{20}ClNO_2$	62.33	62.30	7.47	7.37			5.19	5.23
18	OH	CH_3	*o*-OCH_3	H				190(B)	$C_{14}H_{22}ClNO_2$	61.86	62.03	8.16	7.93			5.15	5.10
19	=O	CH_3	*p*-OCH_3	H	A			197–199(B, dec.)	$C_{14}H_{20}ClNO_2$	62.33	62.19	7.47	7.42	13.14	13.12	5.19	5.40
20	OH	CH_3	*p*-OCH_3	H				204(B)	$C_{14}H_{22}ClNO_2$	61.87	61.59	8.16	8.30	13.05	12.95	5.17	5.16
21	=O	CH_3	3,4-di$OCH_2C_6H_5$	H	A			210–212(B)	$C_{27}H_{32}ClNO_3$	71.43	71.48	7.11	6.71	7.81	7.89	3.09	3.19
22	OH	CH_3	3,4-diOH	H				189–190(B)	$C_{13}H_{20}ClNO_3$	57.03	56.92	7.33	7.36	12.95	12.94	5.12	4.99
23	=O	C_6H_5	H	H	D[n]			218–220(B)	$C_{18}H_{20}ClNO$	71.63	71.67	6.68	6.79	11.85	11.79	4.64	4.79
24	OH	C_6H_5	H	H	[k]			248–249(B)	$C_{18}H_{22}ClNO$	71.15	71.04	7.30	7.22	11.67	11.68	4.61	4.68
25	OH	*o*-$C_6H_4OCH_3$	*o*-OCH_3	H	D			227–228(B)[o]	$C_{20}H_{26}ClNO_3$	66.01	66.15	7.20	6.96	9.74	9.68	3.85	4.10
26	=O	*p*-$C_6H_4OCH_3$	*p*-OCH_3	H	D			225–227(T)	$C_{20}H_{24}ClNO_3$	66.38	66.53	6.69	6.71	9.80	9.76	3.87	4.07
								216(B)									
27	OH	*p*-$C_6H_4OCH_3$	*p*-OCH_3	H	[k]			215–216(B)	$C_{20}H_{26}ClNO_3$	66.01	66.20	7.20	6.88	9.74	9.63	3.85	3.93

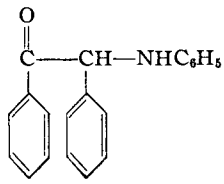
[a] Uncorrected. T = tube, B = Fisher–Johns block. [b] $n^{20}D$ 1.5290. [c] $n^{20}D$ 1.5223. [d] $n^{20}D$ 1.5608. [e] Mixture of diastereoisomers. [f] $n^{20}D$ 1.5611. [g] $n^{20}D$ 1.5619. [h] Picrate. Hydrochloride could not be obtained crystalline. [i] Neither method B nor C gave the desired product. [j] =O here and elsewhere indicates the aminoketone which on reduction gave the aminoalcohol. [k] Reduction of the aminoketone was carried out with $LiAlH_4$. [l] Method B gave a product which could not be crystallized. [m] For the picrate. The hydrochlorides of 15 and 16 did not analyze well for carbon. [n] Method B gave hydrobenzoin. With method C hydrogen uptake was only slight. [o] The aminoketone hydrochloride could not be obtained crystalline so the crude base was reduced with $LiAlH_4$.

Table I shows, method B[5] was not successful when R′ was either CH_3 or C_6H_5. In the former case hydrogen was absorbed but no solid material could be obtained, while in the latter case only hydrobenzoin was isolated. Method C was unsuccessful in the one case tried (R = C_6H_5); no hydrogen was absorbed. Thus the presence of the additional carbonyl function appeared to have a profound effect on the reactivity of the carbonyl group involved in this reaction. Method D[6] is an adaptation of the Voigt reaction and represents the first instance, of which the authors are aware, in which secondary amines have been employed.

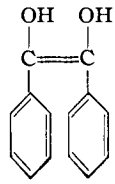
Voigt[7] studied the condensation of benzoin with aniline and, postulating the product to be a Schiff base I, concluded that the reaction would be limited to primary amines. Cameron, Nixon and Basterfield,[8] however, showed that Voigt's prod-



I



II



III

uct was, in fact, the aminoketone II, and proposed that benzoin reacted in the form of an enediol III with subsequent loss of water. On the other hand Cowper and Stevens,[9] using ring-substituted benzoins, were able to show that condensation occurred at the carbonyl function. On this basis they inferred that the initial product was the anil I which then isomerized to II. As confirmation of this sequence they cited the failure of the secondary amine methylaniline to condense even under more drastic conditions. The most recent discussion of the mechanism of this reaction was that of Lutz, Freek and Murphey[6] who concurred with Cowper and Stevens. They used the Voigt reaction to prepare a series of secondary aminoketones but resorted to other methods for the synthesis of the corresponding tertiary aminoketones.

Our attempts to condense diethylamine with benzoin under the conditions of the Voigt reaction met with failure, the benzoin being recovered unchanged. However, when pyrrolidine and piperidine were used, the corresponding tertiary aminoketones were isolated in fairly good yields. In view of the work of Cowper and Stevens,[9] the mechanism outlined in Fig. 2 seems most feasible for this reaction.

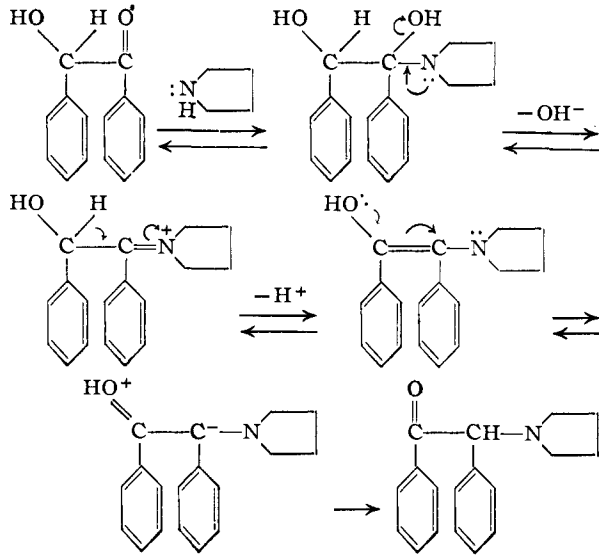


Fig. 2.

Conversion of the aminoketones to the corresponding aminoalcohols was carried out by catalytic hydrogenation or by means of lithium aluminum hydride.[10]

Pharmacology.[11]—Among the compounds in which R′ is H or CH_3 (Table I), Compound no. 14 with a catechol ring system is less pressor and less bronchodilator than epinephrine but qualitatively resembles the latter in its pressor effect. Compound no. 22 is also somewhat pressor but of short duration. The remaining compounds in this paper are either depressor or have no effect on blood pressure. Those members in which R is H or OH are in general good-to-excellent bronchodilators as measured by the Sollmann, von Oettingen isolated lung technique,[12] except where R′ is H in which case the activity is somewhat diminished. In general, compounds in which a carbonyl group appears beta to the nitrogen atom show only a low order of activity.

α,β-Diphenethylamines have been studied widely for a variety of biological effects.[13] Considerable interest has been aroused concerning possible antimitotic activity,[6] and many compounds have been tested by the National Cancer Institute for their

(5) R. H. F. Manske and T. B. Johnson, THIS JOURNAL, **51**, 580, 1906 (1929); U. S. Patent 1,799,110; German Patents 603,670, 634,002.

(6) R. E. Lutz, J. A. Freek and R. S. Murphey, THIS JOURNAL, **70**, 2015 (1948).

(7) K. Voigt, *J. prakt. Chem.*, [2] **34**, 2 (1886).

(8) C. N. Cameron, A. C. Nixon and S. Basterfield, *Trans. Roy. Soc. Can.*, **3**, 25, Sept. 3, 145 (1931).

(9) R. M. Cowper and T. S. Stevens, *J. Chem. Soc.*, 347 (1940).

(10) In those cases where the compounds being reduced were substituted benzylamines, there was no indication of catalytic debenzylation; hydrogen uptake slowed up toward the end and was essentially stopped when the calculated end-point had been reached. As emphasized by the referee the catalytic hydrogenation of the optically active aminoketones would be expected to result in aminoalcohols of the ephedrine form. Use of $LiAlH_4$, on the other hand, has been known to be non-specific in that it sometimes results in *erythro–threo* mixtures (*e.g.*, H. Felkin, *Compt. rend.*, **231**, 1316 (1950)), and sometimes produces either the same or opposite configuration as the catalytic method (see for example, M. E. Speeter, *et al.*, THIS JOURNAL, **71**, 57 (1949); D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950). This uncertainty of configuration makes pharmacological evaluation of compounds 24, 25 and 27 difficult.

(11) We are grateful to Dr. Milton J. VanderBrook and B. E. Graham of our Department of Pharmacology for permission to publish this brief summary of their work.

(12) T. Sollmann and W. F. von Oettingen, *Proc. Soc., Exptl. Biol. Med.*, **25**, 692 (1928).

(13) For example, M. L. Tainter, F. P. Luduena, R. W. Lackey and E. N. Neuru, *J. Pharmacol.*, **77**, 317 (1943).

effect on tumor growth.[14] Reports have also appeared on their antispasmodic[15] and analgetic[16] activities. However, very few examples of tertiary amines have been reported,[1i] and little if any work has been published as to bronchodilator properties of compounds of the α,β-diphenethylamine type.[17]

Many of the compounds reported here belonging to this class are very effective bronchodilators, and several are currently under clinical trial.

Experimental[18]

N-[β-(*o*-Methoxyphenyl)-isopropyl]-pyrrolidine Hydrochloride. (Method B, Compound 2).—Eighty-two grams (0.5 mole) of *o*-methoxyphenylacetone[1h] and 35.5 g. (0.5 mole) of anhydrous pyrrolidine were dissolved in 75 ml. of anhydrous ethanol. The solution was placed in a Parr hydrogenation apparatus with 0.5 g. of Adams platinum oxide catalyst and subjected to hydrogenation at three atmospheres hydrogen pressure. After four hours the calculated amount of hydrogen had been absorbed. The oil obtained after removal of the solvent was distilled *in vacuo;* b.p. 118° at 0.5 mm., yield 98.5 g. (90%), $n^{20}D$ 1.5290.

The colorless oil was dissolved in 200 ml. of acetone and 60 cc. of absolute ethanol containing an equivalent amount of hydrogen chloride was added with stirring and cooling. After half the acid had been added a seed crystal was introduced into the flask, and soon thereafter colorless crystals began to deposit. These were filtered, washed with ether and dried; wt. 43.5 g., m.p. 152–153.5°. Addition of more ether to the filtrate and further chilling gave an additional 45.5 g. of product, m.p. 152–153°; total yield 89 g. (70% over-all).

The above 89 g. of material was recrystallized by dissolving in 1.5 parts of isopropyl alcohol and adding 2 parts of acetone and 10 parts of anhydrous ether. After chilling, the white crystals were filtered and dried; wt. 77 g. Their properties are listed in Table I.

N-[β-(*o*-Methoxyphenyl)-isopropyl]-2-phenylpyrrolidine Hydrochloride (Method B, Compound 6).—Eight and two tenths grams (0.05 mole) of *o*-methoxyphenylacetone[1h] and 7.25 g. (0.05 mole) of 2-phenylpyrrolidine[19] ($n^{20}D$ 1.5560) were dissolved in 50 ml. of absolute methanol and were subjected to hydrogenation as described for compound 2. Hydrogenation was complete in about two hours. The oil obtained after removal of the solvent was distilled *in vacuo* to give 11.5 g. (78%) of the desired amine. This material was dissolved in 50 ml. of dry ether, and a solution of 1.5 g. of hydrogen chloride gas in 5 ml. of anhydrous ethanol was added with cooling. After further cooling and scratching there was obtained 12 g. of a slightly gummy solid. This crude product was recrystallized by dissolving in 1.75 parts of boiling isopropyl alcohol, decolorizing with charcoal and adding 1.75 parts of acetone and 6 parts of ether. On seeding there was at once deposited 8.5 g. of white crystals, m.p. 171–184°. Addition of more ether to the filtrate, followed by chilling gave a second crop, 1.5 g., m.p. 180–185°. The main crop represented a mixture of diastereoisomers and no attempt was made to separate them. However, two more recrystallizations of a portion of this gave a product melting at 194–200° which gave the analysis indicated in Table I.

N-(α,β-Diphenylethyl)-pyrrolidine Hydrochloride (Method C, Compound 8).—With stirring 39.2 g. (0.2 mole) of desoxybenzoin, 17 g. (0.24 mole) of pyrrolidine and 30 g. of calcium oxide were heated on the steam-bath for 20 hours. To this was added 100 ml. of anhydrous ethanol and the suspension was filtered. The filtrate was placed in a Parr hydrogenation apparatus, 0.2 g. of Adams platinum oxide catalyst was added and hydrogenation continued at three atmospheres hydrogen pressure till the calculated amount of hydrogen had been absorbed. The oil obtained after removal of the solvent was distilled *in vacuo*, and the resulting amine was dissolved in ethyl acetate. A slight excess of ethanolic hydrogen chloride was added to precipitate the hydrochloride. The latter was recrystallized from a mixture of ethanol and ethyl acetate to yield a product having the properties indicated in Table I.

N-[β-Hydroxy-β-(3,4-dihydroxyphenyl)-ethyl]-pyrrolidine Hydrochloride (Method A, Compound 14).—3,4-Dihydroxy-α-chloroacetophenone[20] (18.6 g., 0.1 mole) and pyrrolidine (28.4 g., 0.4 mole) were dissolved in 100 ml. of 98% isopropyl alcohol and heated under reflux for 1.5 hours. Excess hydrogen chloride in isopropyl alcohol was added to the dark, viscous mixture causing 20 g. of a red-brown solid to precipitate. This powdery material was recrystallized from 500 ml. of 3A alcohol[21] and 40 ml. of water to give 16 g. (62%) of colorless crystals, having the properties indicated in Table I.

The above aminoketone hydrochloride was dissolved in water, 10% palladium–charcoal added, and subjected to hydrogenation in a Parr apparatus at 60° and three atmospheres pressure. The suspension was then filtered, the filtrate evaporated to dryness *in vacuo* and the product recrystallized from ethanol, containing a trace of hydrogen chloride. The almost colorless product slowly turns slightly lavender in the air. Its properties are given in Table I.

N-[β-Hydroxy-β-(*o*-methoxyphenyl)-isopropyl]-pyrrolidine Hydrochloride (Method A, Compound 18).—To a stirred solution of 48 g. (0.17 mole) of *o*-methoxy-α-bromopropiophenone[1h] in 350 ml. of chloroform 55 g. (0.77 mole) of pyrrolidine was added dropwise. Stirring was continued for three hours at room temperature and one hour under reflux. The product was washed with water, dried over sodium sulfate and the solvent was removed *in vacuo*. The oil was dissolved in anhydrous ether and dry hydrogen chloride gas was passed into the solution. The ether was decanted from the red gum, 25 ml. of ethyl acetate was added and the gum scratched until it became solid. This was recrystallized by dissolving in absolute ethanol and adding ether. After chilling 15 g. (33%) of pure crystalline material was obtained having the properties indicated in Table I.

The above aminoketone hydrochloride (15 g.) was dissolved in 75 ml. of water and subjected to hydrogenation at 75° and three atmospheres hydrogen pressure with 2 g. of active palladium charcoal as the catalyst. Hydrogen uptake was slow but complete. The catalyst was filtered off and the filtrate evaporated to dryness *in vacuo* to give a white solid which was dissolved in anhydrous ethanol. On chilling, a white crystalline product was deposited having the properties indicated in Table I. Addition of ether to the filtrate yielded a second crop, m.p. 190° (block).

The above procedure was repeated with the following variations. The bromoketone was added to pyrrolidine in ether without heating, and the resulting aminoketone was reduced directly with lithium aluminum hydride in the usual way. By this procedure the yield of crystalline aminoalcohol hydrochloride from the bromoketone was 30%. An additional 10% resisted crystallization.

In another experiment the bromopropiophenone was prepared in chloroform; the resulting solution was washed with water and used directly for the reaction with pyrrolidine at room temperature. The crude aminoketone was reduced directly with lithium aluminum hydride to give a 30% yield of the aminoalcohol hydrochloride.

N-[β-Hydroxy-(3,4-dihydroxyphenyl)-isopropyl]-pyrrolidine Hydrochloride (Method A, Compound 22).—Ten grams (0.14 mole) of pyrrolidine was added dropwise to a rapidly stirred solution of 30 g. (0.07 mole) of 3,4-dibenzyloxy-α-bromopropiophenone[22] in dry benzene. The mixture was stirred overnight, washed with water and the benzene

(14) M. J. Shear, Abstracts, First National Medicinal Chemistry Symposium of the American Chemical Society, Ann Arbor, June, 1948, p. 87.

(15) K. W. Rosenmund and F. Kulz, U. S. Patent 2,006,114.

(16) E. J. Fellows, Abstracts, First National Medicinal Chemistry Symposium of the American Chemical Society, Ann Arbor, June, 1948, p. 35; H. G. O. Holck, K. K. Kimura and T. E. Kimura, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 354 (1950).

(17) Tainter and co-workers[13] reported a group of primary and secondary amines of this type but rated them of no interest as bronchodilators.

(18) Analyses are by W. A. Struck and staff of our Microanalytical Laboratory.

(19) L. C. Craig, H. Bulbrook and R. M. Hixon, THIS JOURNAL, **53**, 1831 (1931).

(20) N. Levin and W. H. Hartung, *J. Org. Chem.*, **7**, 408 (1942); PB Rep. 32536.

(21) 90% ethanol, 5% methanol, 5% water.

(22) Kleiderer, Rice, Conquest, Williams, Report No. PB-981, Office of Publication Board, Department of Commerce, Washington, D. C.

removed *in vacuo*. The resulting free base was dissolved in ethyl acetate and with stirring and cooling ethanolic hydrogen chloride was slowly added. The tan powder which precipitated was recrystallized from 3A alcohol to yield 24 g. (76%) of colorless crystals with the properties indicated in Table I.

The aminoketone hydrochloride was simultaneously debenzylated and converted to the aminoalcohol in aqueous solution using a Parr apparatus at 60° and palladium–charcoal as the catalyst. The filtrate from the catalyst was evaporated *in vacuo* to dryness and the product recrystallized from a mixture of ethanol and ether. It had the properties indicated in Table I.

N-[β-Hydroxy-α,β-diphenylethyl]-pyrrolidine Hydrochloride (Method D, Compound 24).—Twenty-one and two tenths grams (0.1 mole) of benzoin, 7.1 g. (0.1 mole) of pyrrolidine and 2 g. of phosphorus pentoxide were mixed and heated on a steam-bath for four hours. The cooled product was triturated with ether, the ether extracted with dilute hydrochloric acid and the acid solution was treated with decolorizing charcoal and filtered. The filtrate was basified with sodium hydroxide and extracted with ether. The ether layer was washed with water and dried, and to it was added a slight excess of ethanolic hydrogen chloride. The solid product was recrystallized from an ethanol–ether mixture to give 18 g. (60%) of colorless crystals with the properties indicated in Table I.

The above aminoketone hydrochloride was converted to the free base in ether and the ether solution dried. This solution (200 ml.) was added dropwise to a well-stirred and refluxing solution of 6 g. of lithium aluminum hydride in 200 ml. of dry ether. After the addition was complete, stirring and heating were continued for half an hour, after which time 25 ml. of water was added very carefully dropwise with cooling in an ice-bath. The mixture was poured into one liter of 10% sodium hydroxide solution, extracted with ether and the ether was washed and dried over sodium sulfate. The solvent was removed *in vacuo*, the product dissolved in ethyl acetate and a slight excess of ethanolic hydrogen chloride was added. The white crystalline solid was recrystallized from an ethanol–ether mixture to give 9 g. (50%) of colorless crystals having the properties indicated in Table I.

N-[β-Hydroxy-α,β-diphenylethyl]-piperidine Hydrochloride (Method D).—Following the procedure described above for the synthesis of α-pyrrolidyl-α-phenylacetophenone, piperidine was condensed with benzoin using a catalytic amount of phosphorus pentoxide. The solid free base of the resulting α-piperidyl-α-phenylacetophenone was isolated and recrystallized several times from 80% 3A alcohol, m.p. 82–84°, 57% yield. Lutz, Freek and Murphey[6] reported m.p. 82–83° (from desyl chloride and piperidine).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01. Found: C, 81.85; H, 7.64; N, 5.02.

The hydrochloride was prepared by dissolving the free base in ethyl acetate and adding excess ethanolic hydrogen chloride. The gummy precipitate was recrystallized several times from ethanol–ether, m.p. 236–238° (dec.). Lutz, Freek and Murphey[6] reported m.p. 225–227° (dec.) while Goodson and Moffett[23] reported m.p. 239–242° (from desyl bromide and piperidine).

In an attempt to catalytically reduce α-piperidyl-α-phenylacetophenone hydrochloride to N-[β-hydroxy-α,β-diphenylethyl]-piperidine hydrochloride in water over 10% palladium charcoal, the hydrogen uptake started slowly but after four hours had rapidly advanced to 150% of theory. At this point the catalyst was removed and an oily layer was extracted out with benzene. Distillation of the benzene left a yellow oil with neutral odor, probably benzyl phenylcarbinol. Basification of the aqueous portion liberated a strong amine odor, probably piperidine. Extraction of the basic aqueous portion with ether, followed by addition of ethanolic hydrogen chloride yielded an oil and a solid. The oil was probably the very soluble piperidine hydrochloride while the solid had m.p. 236–237° (dec.) corresponding to the starting material.

In the same manner as the reduction of the α-pyrrolidyl-α-phenylacetophenone described above, the α-piperidyl-α-phenylacetophenone was reduced chemically with lithium aluminum hydride. The solid free base was isolated and recrystallized from 90% 3A-alcohol, m.p. 108–110°. Lutz, Freek and Murphey[6] reported m.p. 109–110° (aluminum isopropoxide reduction).

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.09; H, 8.23; N, 4.98. Found: C, 81.50; H, 8.22; N, 4.91.

The hydrochloride was prepared by dissolving the free base in ethyl acetate and adding excess ethanolic hydrogen chloride. It was recrystallized several times from an isopropyl alcohol–methanol mixture, m.p. 255–257°. Lutz, Freek and Murphey[6] reported m.p. 259–260°, while Goodson and Moffett[23] reported m.p. 240–243° (also aluminum isopropoxide reduction).

Anal. Calcd. for $C_{19}H_{24}ClNO$: C, 71.79; H, 7.61; N, 4.41; Cl, 11.16. Found: C, 71.86; H, 7.66; N, 4.27; Cl, 11.14.

(23) L. H. Goodson and R. B. Moffett, THIS JOURNAL, **71**, 3219 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

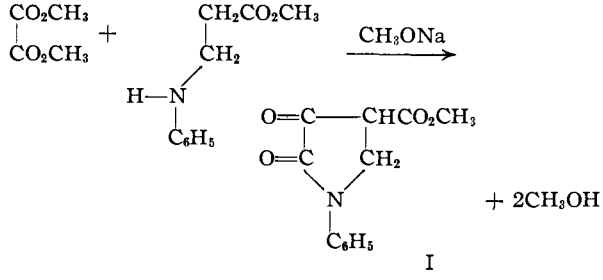
The Condensation of Oxalic Esters with Esters of β-Alanine and N-Substituted β-Aminopropionic Acids. Synthesis of Some Derivatives of 2,3-Dioxopyrrolidine and 2-Oxo-3-methoxy-3-pyrroline

BY PHILIP L. SOUTHWICK AND ROBERT T. CROUCH[1]

RECEIVED MARCH 18, 1953

The condensation of methyl or ethyl oxalate with a series of N-substituted β-aminopropionic esters has yielded a series of 4-carbomethoxy and 4-carbethoxy-2,3-dioxopyrrolidines with phenyl, *p*-tolyl, *m*-chlorophenyl, *p*-methoxyphenyl, benzyl and cyclohexyl groups at position 1. A similar compound unsubstituted in position 1 is also described. The dioxopyrrolidines were converted into 4-carboalkoxy-2-oxo-3-methoxy-3-pyrrolines by treatment with diazomethane. The 4-carboalkoxy-1-benzyl-2,3-dioxopyrrolidines were hydrolyzed and decarboxylated to 1-benzyl-2,3-dioxopyrrolidine.

In a recent publication[2] from this Laboratory a synthesis was described for the compound 4-carbomethoxy-1-phenyl-2,3-dioxopyrrolidine (I)[3] by means of the condensation of methyl oxalate with methyl β-anilinopropionate in the presence of sodium methoxide



I

(1) Du Pont Fellow in Chemistry, 1951–1952.

(2) P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2532 (1949).

(3) Referred to as 1-phenyl-4-carbomethoxy-2,3-pyrrolidinedione in ref. 2.