Sympathomimetics: 2,3-Diphenylpropylamines[1]

By Albert M. Mattocks[2] and Olivia S. Hutchison

The sympathomimetic group of drugs is composed largely of phenylethylamines with various substituents on both the aromatic and aliphatic portions of the molecule. It has often been found that the addition of a methyl group to either carbon of the aliphatic chain of phenethylamine derivatives yielded compounds with improved pressor activity (*i. e.*, amphetamine, propadrine, ephedrine), but the effect produced by introduction of radicals larger than methyl in these positions has not been extensively studied. It was believed important that such substitutions be investigated since it is possible that compounds with more prolonged pharmacological action might result.

For initial studies 2,3-diphenylpropylamines, compounds that may be regarded as 2-aralkylphenethylamines, were synthesized.

2,3-Diphenylacrylonitriles (prepared by the procedure of Knoevenagel[3] in glacial acetic acid solution were smoothly hydrogenated to diphenylpropylamines in a Parr low-pressure hydrogenator using platinum oxide catalyst. The products were isolated in yields varying from 58–72%. 2-Phenyl-3-(4-hydroxyphenyl)-propylamine and 2-phenyl-3-(3,4-dihydroxyphenyl)-propylamine were obtained from the corresponding methoxy and methylenedioxy amines by hydrolysis with hydriodic acid. These compounds were extracted as free bases and converted into hydrochlorides with alcoholic hydrogen chloride.

Experimental

2,3-Diphenylacrylonitriles.—One mole of benzyl cyanide, one mole of benzaldehyde, and 15 cc. of piperidine were mixed and heated at 100° for thirty-six hours. While hot, the mixture was poured into a beaker and stirred occasionally until it had crystallized. The crystals were washed free of unreacted materials on a filter and recrystallized from glacial acetic acid. The recrystallized product was air-dried. 2,3-Diphenyl-,[3] 2-phenyl-3-(4-methoxyphenyl)-,[4] and 2-phenyl-3-(3,4-methylenedioxyphenyl)-acrylonitriles were obtained in yields of 86, 42 and 43%, respectively. The latter compound, not previously synthesized, melted at 115–116°, and its empirical formula was proved by analysis.

Anal. Calcd. for $C_{16}H_{12}O_2N$: C, 73.90; H, 4.38. Found: C, 73.90, 74.11; H, 4.42, 4.40.

2,3-Diphenylpropylamines.—Five-hundredths mole of diphenylacrylonitrile was dissolved in 100–200 cc. of glacial acetic acid; 0.5 g. of platinum oxide catalyst was added and the mixture shaken in a Parr low-pressure hydrogenator at an initial pressure of 40 pounds. After the calculated amount of hydrogen was absorbed (usually after five to six hours), the reaction mixture was removed and filtered. Most of the acetic acid was distilled off under vacuum, and the residue was made strongly basic with 30% sodium hydroxide. The free amine was extracted with ether and fractionally distilled at reduced pressure through a Vigreux column.

Table I

Diphenylpropylamines, $RCH_2CH(C_6H_5)CH_2CH_2$

R	Yield, %	B. p. Free °C.	B. p. base Mm.	M. p. HCl, °C.	Form analyzed	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
C_6H_5-[a]	58	105–108	0.5	189–190	HCl					5.65	5.60, 5.57
3,4-$CH_2O_2C_6H_3$-	61	176–178	1		Base	75.27	74.86, 75.20	6.71	6.97, 6.99	5.49	5.44, 5.59
4-$CH_3OC_6H_4$-	72	168–172[b]	2		Base	79.63	79.62, 79.72	7.94	8.42, 7.86	5.80	5.65, 5.87
3,4-$(HO)_2C_6H_3$-	42			183–184	HCl	64.39	64.08, 64.04	6.49	6.30, 5.39	5.01	4.96, 5.03
4-HOC_6H_4-	55			212–214	HCl					5.31	5.34, 5.36

[a] Previously synthesized in 15% yield.[5] [b] M. p. 42°.

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(5) M. Freund and P. Remse, *Ber.*, **23**, 2859 (1890).

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(1) The authors gratefully acknowledge the assistance of Maxine B. Thomas who aided in a portion of the syntheses and of Mathilde Ramsey who performed the analyses.

(2) Present address: Western Reserve University, School of Pharmacy, Cleveland, Ohio.

(3) E. Knoevenagel, German Patent 94,132, July 23, 1895.

(4) H. V. Frost, *Ann.*, **250**, 156 (1889).

Storage Effects on the Proteins of Peanuts

By T. A. Pickett

Jones and Gersdorff[1] reported that after six months storage of soybean meal at 30° and 76° F. the solubility of the proteins in salt solution decreased. Other workers[2,3] found no change in solubility of the proteins in cottonseed after prolonged storage at a wide range of temperatures.

As the results reported on cottonseed and soybeans are in marked contrast and as practically all harvested peanuts, whether in the shell, shelled or as meal, are stored under variable conditions, a study was made in order to determine the effects of storage on peanut proteins. Protein solubilities were determined on whole, shelled, hydraulic pressed and solvent-extracted Spanish peanuts. The samples were air-dried and stored in the dark at 33°F. and both in the dark and light at 75 ± 10°F. At intervals up to three years the peanuts were shelled, extracted with Skellysolve F, finely ground, and the solubilities of the proteins in water were determined on all the samples using the Smith, Circle and Brother procedure.[4] After storing three years at 33°F. and in the dark and

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(1) D. B. Jones and C. E. F. Gersdorff, This Journal, **60**, 723 (1938).

(2) H. S. Olcott and T. D. Fontaine, *ibid.*, **62**, 3519 (1940).

(3) M. F. Stansbury and J. D. Guthrie, *J. Agr. Research*, **75**, 49 (1947).

(4) A. K. Smith, S. J. Circle and G. H. Brother, This Journal, **60**, 1316 (1938).

light at 75°F. the solubility of the proteins was the same, within the range of experimental error (±1.0%) as at the beginning of the experiment for all samples of whole peanuts, shelled peanuts, and solvent extracted meals.

The solubility of the proteins in hydraulic meal showed no significant change when stored at 33°F. for three years; however, after one year in the dark and light at 75°F. the solubility dropped from 79.7 to 76.4 and 76.6%, and after three years to 72.9 and 70.5%, respectively. Although rancidity was observed in the samples showing changes in protein solubility, no further investigations were made. All other samples which did not change in protein solubility after storage were either not noticeably rancid or the proteins were extracted from oil-free meals; thus it is possible that changes in the residual lipids were responsible for the changes in solubility of proteins in the hydraulic meals stored at 75°F.

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The Reaction of Thioglycolamide with Halomethyl Ketones

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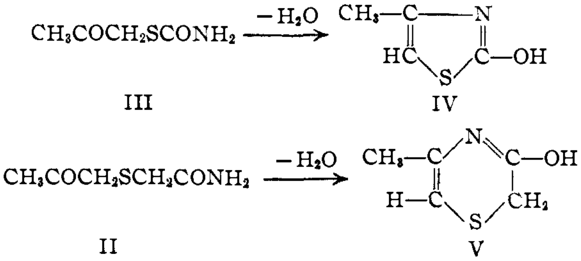
The unusual reactivity of the mercapto group in thioglycolamide was first noted by Klason and Carlson[2] when they observed the rapidity with which it was oxidized to the bis-disulfide on exposure to air. There do not however appear to be any other references in the literature to the lability of thioglycolamide.

We have found that thioglycolamide reacts with halomethyl ketones with striking vigor to liberate hydrogen halide. With chloroacetone, reaction occurred spontaneously on mixing the two reactants at room temperature; considerable heat was evolved. Reaction with phenacyl bromide was initiated by warming to 50°. Hydrogen bromide was evolved and S-phenacylthioglycolamide (I) was isolated in good yield. It was hydrolyzed

$$C_6H_5COCH_2Br + HSCH_2CONH_2 \longrightarrow \underset{\text{I}}{C_6H_5COCH_2SCH_2CONH_2} + HBr$$

to S-phenacylthioglycolic acid, which has been previously described.[3]

The product obtained from the reaction of thioglycolamide and chloroacetone was not S-acetonylthioglycolamide (II). Analysis indicated the loss of a molecule of water with the formation of *anhydro*-S-acetonylthioglycolamide. This compound was soluble in cold dilute hydrochloric and acetic acids with cleavage to the open-chain compound, and liberated ammonia on boiling with 10% sodium hydroxide. In aqueous acid solution it formed a 2,4-dinitrophenylhydrazone which analyzed correctly for that of II. It is interesting to note that II is the next higher homolog of S-acetonylthiocarbamate (III) which readily loses one molecule of water to form 2-hydroxy-4-methylthiazole (IV).[4] By analogy a possible structure (V) is suggested for *anhydro*-S-acetonylthioglycolamide.



Experimental[5]

Thioglycolamide.—Anhydrous ammonia gas was bubbled slowly through 212 g. of methyl thioglycolate (b. p. 49–51° at 16 mm.) for twenty-four hours. The reaction mixture became warm and its viscosity increased markedly. It was transferred to a desiccator and the methanol removed under vacuum. There was obtained 175 g. (96%) of crude amide as a white amorphous powder. It was stored under nitrogen and used directly without purification.

S-Phenacylthioglycolamide.—A mixture of 20 g. of phenacyl bromide and 9 g. of thioglycolamide was warmed to 50°. A vigorous reaction occurred liberating copious quantities of hydrogen bromide. When evolution of the gas ceased, 100 g. of ice and water were added to the dark reaction mixture and a mass of brown crystals separated. The crude material was filtered and recrystallized from ethanol yielding 16 g. (76%) of sparkling white leaflets, m. p. 157–158°.

Anal. Calcd. for $C_{10}H_{11}O_2NS$: N, 6.70; S, 15.31. Found: N, 6.68; S, 15.39.

S-Phenacylthioglycolic Acid.—One gram of S-phenacylthioglycolamide was boiled for five minutes with 15 ml. of 20% hydrochloric acid; the solid dissolved slowly. The hot solution was filtered and cooled to give 0.7 g. of the acid. Recrystallization from water gave white needles, m. p. 100–101°.[3]

Anal. Calcd. for $C_{10}H_{10}O_3S$: S, 15.24; neut. equiv., 210. Found: S, 15.34; neut. equiv., 207.

Reaction of Chloroacetone with Thioglycolamide.—To 9 g. of thioglycolamide was added 9.3 g. of chloroacetone. A vigorous evolution of hydrogen chloride occurred spontaneously and a clear, viscous solution resulted. After five minutes, 50 g. of ice and water were added to the warm reaction mixture and the precipitate filtered and recrystallized from ethanol to give 12 g. (93%) of beautiful white platelets, m. p. 144°.

Anal. Calcd. for C_5H_7ONS: C, 46.50; H, 5.42; N, 10.85; S, 24.80. Found: C, 46.61; H, 5.48; N, 10.76; S, 24.85.

The 2,4-dinitrophenylhydrazone, prepared in aqueous solution, was recrystallized from ethanol, m. p. 159–161°.

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[2] Klason and Carlson, *Ber.*, **39**, 763 (1906).

[3] Behaghel and Schneider, *Ber.*, **68**, 1591 (1935).

[4] Tcherniac, *J. Chem. Soc.*, **115**, 1076 (1919); Hantzsch, *Ber.*, **60**, 2537 (1927).

[5] Melting and boiling points uncorrected.