

Anal. Calcd. for $C_{20}H_{21}O_5N_3$ (431.39): C, 55.7; H, 4.9. Found: C, 55.6; H, 5.0.

2-Phenyl-2,1,3-triazole-4,5-dicarboxaldehyde (III). II (288 mg., 1.1 mmole) was shaken at room temperature with 10 ml. of aqueous sodium metaperiodate (755 mg., 3.55 mmole). During 24 hr., the silky needles of osotriazole changed to shorter, thicker crystals. The product, obtained by filtration, was cream white and had a perfume-like odor. (2-Phenyl-2,1,3-triazole-4-carboxaldehyde smells like geraniol.⁷) After two recrystallizations from ethanol-water, it weighed 164 mg. (75% yield) and melted at 145–147°. The compound sublimes readily.

Titration of aliquots of the original filtrate showed that slightly over 3 molar equivalents of periodate had been consumed with the production of exactly 2 molar equivalents of acid, as required for the removal of 2 carbon atoms from II to give a triazole dialdehyde.

The aldehyde gave a 2,4-dinitrophenylhydrazone (presumably the bis derivative) melting at 304–307° (dec.). Final identification of the aldehyde was made by oxidizing it with neutral permanganate to an acid which, after recrystallization from 30% acetic acid containing a few drops of conc. HCl, had the properties of the known *2-phenyl-2,1,3-triazole-4,5-dicarboxylic acid*. [Found: Neutral equivalent⁸; 126; m.p., 259–261° (dec.). Lit.:⁹ Neutral equivalent, 116.5, m.p., 255–256° (dec.).]

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Some Reactions Leading to 8-Aminocaffeine

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8-Aminocaffeine is an important intermediate in the preparation of certain pharmacologically useful compounds. It has been prepared previously by three different methods and each method has certain disadvantages. The earliest and still most widely used method is due to Fischer,¹ who prepared this compound by heating 8-bromocaffeine with ammonia under pressure. Yields are excellent, but the method is not convenient for the laboratory preparation of moderate amounts of compound. Two other reports exist in the literature for the preparation of 8-aminocaffeine. The second is by Brooks and Rudner,² who reported that caffeine reacts with chloramine to give a low yield of a product which was thought to be 8-aminocaffeine; and

the third is by Burgison and Wilson,³ who obtained 8-aminocaffeine by reducing 8-nitrotheophylline to 8-aminotheophylline. Methylation of this compound yielded 8-aminocaffeine. The over-all yield for this latter method has not been reported.

We have prepared 8-aminocaffeine by two different routes. The first was by a Gabriel synthesis from 8-bromocaffeine using dimethylformamide as a solvent. This, in itself, would not be an improvement over the Fischer synthesis of this compound, as, generally, the *N*-substituted phthalimides have to be hydrolyzed in a sealed tube. In this case, however, hydrolysis was effected very easily by heating the *N*-(8-caffeinyloxy)phthalimide for a short period of time with dilute acid at atmospheric pressure. The second method consisted in heating 8-caffeinyldiazine in either phenol or dimethylformamide solution. This latter reaction was discovered when an attempt to prepare 1,6-di(8-caffeinyloxy)-1,2,5,6-tetrahexane from the reaction of 8-caffeinyldiazine with ethylene bromide led unexpectedly to the formation of 8-aminocaffeine.

Although the yields in these reactions are not high, they do represent relatively simple laboratory methods of preparing 8-aminocaffeine. The second method is considered preferable since 8-caffeinyldiazine can be obtained in quantitative yield from the reaction of 8-bromocaffeine with hydrazine hydrate and 8-caffeinyldiazine can be converted to 8-aminocaffeine in 40–43% yield while the Gabriel synthesis resulted in only a 24% yield of 8-aminocaffeine.

EXPERIMENTAL

Microanalyses are by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mulheim/Ruhr, Germany.

Gabriel Reaction. A mixture of 82 g. of 8-bromocaffeine (0.3 m.), 88 g. of phthalimide (0.6 m.), 56 g. of potassium carbonate and 500 ml. of dimethylformamide was refluxed for 18 hr. During this time the mixture became red and a yellow precipitate formed. The yellow precipitate was then dissolved in dilute hydrochloric acid and the solution refluxed for 15 min. After cooling and making the solution basic a white precipitate was obtained which was recrystallized from an ethanol-acetic acid mixture. The yield was 15 g. (24%) of white powder, m.p. >320°.

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30. Found: C, 45.95; H, 5.55.

Reaction of 8-caffeinyldiazine in dimethylformamide. A solution of 3.5 g. of 8-caffeinyldiazine in 100 ml. of dimethylformamide was refluxed for 14 hr. The solution became dark red in color. After cooling to -20°, 1.3 g. of a green precipitate were collected which after recrystallization from an ethanol-acetic acid mixture gave 0.7 g. of a tan product, m.p. >320°. This compound was identified as 8-aminocaffeine by the characteristic triplet peak it exhibited in the *N*-H region of the infrared and conversion to the known 8-diacetamidocaffeine. The yield was 40% before recrystallization.

(1) E. Fischer, *Ann.*, **215**, 253 (1882).

(2) M. E. Brooks and B. Rudner, *J. Am. Chem. Soc.*, **78**, 2339 (1956).

(3) R. M. Burgison and H. F. Wilson, Abstract of a paper presented before the Medicinal Chemistry Division at the 131st meeting of the American Chemical Society, Miami, April, 1957.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.98; H, 5.39; N, 33.44.

Diacetyl derivative, m.p. 137–142°; mixture m.p. with authentic 8-diacetamidocaffeine, 137–142°.

Reaction of 8-Caffeinyldiazine with ethylene bromide. A stream of nitrogen was passed through a solution of 10 g. of 8-caffeinyldiazine (0.045 m.) in 350 ml. of dimethylformamide as it was heated to reflux and while it was refluxing. To this refluxing solution was added 4.5 g. of ethylene bromide (0.024 m.) in 30 ml. of dimethylformamide over a period of 1.5 hr. A green precipitate formed after the addition was complete and the solution darkened. The solution was refluxed for 11 hr. and then cooled in an ice-salt bath. A mixture of green and brown precipitates was collected. The combined precipitate was treated with 500 ml. of boiling ethanol. The green precipitate (2.5 g.) remained undissolved and treatment of the ethanol filtrate with hexane gave 1.4 g. of a white precipitate. The green precipitate showed no N—H peak in the infrared and an acid solution of the compound exhibited a peak at 348 $m\mu$ in the ultraviolet. This compound was thought to be 1,2-bis(8-caffeinyldiazine)ethane, m.p. >320°.

Anal. Calcd. for $C_{18}H_{22}N_{12}O_4$: C, 45.95; H, 4.71; N, 35.73. Found: C, 45.99; H, 4.76; N, 35.22.

The tannish-white precipitate was identified as 8-aminocaffeine by its elemental analysis, the characteristic triplet peak it exhibited in the N—H region of the infrared and conversion to the known 8-diacetamidocaffeine. Yield was 15%.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.59; H, 5.55; N, 32.67.

Diacetyl derivative, m.p. 143–146°; mixture m.p. with authentic 8-diacetamidocaffeine, 142–145°.

When this reaction was repeated using phenol as a solvent 8-aminocaffeine was obtained in 43% yield. No 1,2-bis(8-caffeinyldiazine)ethane was found.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 46.37; H, 5.80; N, 32.98.

Diacetyl derivative m.p. 143–145°; mixture m.p. with authentic 8-diacetamidocaffeine, 142–145°.

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Versatility and Temperature Range of Silicone Grease as Partitioning Agent for Gas Chromatography

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Although high vacuum silicone grease has been used rather extensively as partitioning agent in gas chromatography, and column packings containing this material are readily available commercially, there appears to have been published no description of the processing we have found necessary in order to realize the full potential of this partitioning agent. It may be claimed, with some justification, that a properly prepared column containing high vacuum silicone grease as partitioning

agent easily surpasses all others as regards temperature range and variety of compounds that may be satisfactorily chromatographed. Chief limitation to the separations possible is that resolution is based largely on differences in vapor pressure. Major structural differences and differences in functional groups do have significant effects on retention times; however, subtle structural differences and degree of unsaturation usually have little effect on retention times. Even this limitation sometimes becomes an asset when separations on silicone grease are combined with separations on other agents where minor structural differences have larger effects on solubility in the partitioning agent.

There is considerable variation between different commercial¹ lots of high vacuum silicone grease, as regards its performance as a partitioning agent before being conditioned or "cured" at high temperature. Some lots have initially given such extremely long retention times and broad chromatography bands as to be of little use. In all cases, the grease must be heated for a period of at least 50 hours at temperatures above 300° in order to bake out volatile materials. All lots of grease which have been examined have become highly satisfactory as a partitioning agent after being cured as described in the Experimental section. A typical, but by no means maximum, variation between two lots of silicone grease is illustrated in Table I.

TABLE I
CHROMATOGRAPHY OF METHYL ESTERS OF FATTY ACIDS ON SILICONE GREASE^a

Partitioning Agent	Temp. for Chromatog.	Retention Times (min.) for Esters of Acids		
		C ₁₆	C ₁₇	C ₁₈
Lot I, uncured	320°	6.9	8.5	10.4
Lot II, uncured	305°	4.9	6.0	7.5
Lot I, cured ^b	310°	5.1	6.3	7.7
Lot II, cured ^b	305°	3.1	3.8	4.6

^a The partitioning agents were prepared as described in the Experimental section. Chromatography was in a Pyrex glass column, 8 mm. \times 2.5 m.; helium flow was approximately 190 ml./min. ^b Lot I was cured by heating for 8 days at 325–335°; Lot II similarly for 5 days.

The cured silicone grease packing is stable indefinitely when used at temperatures below about 275°. Packings used for several thousand hours have shown essentially constant retention times and unimpaired resolving power. At temperatures near 300°, there is a slow decrease in retention times, and after two thousand hours or longer, resolving power becomes impaired. Most samples of cured grease may be used at 325° for more than 200 hours before the resolving power deteriorates

(1) The silicone grease to which reference is made in this report was purchased from the Dow Corning Corporation, under the name "High Vacuum Grease," during the period 1956–1959.