Densification of Powders by Concavo-Convex Roller Compactor

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Abstract □ By means of a concavo-convex roller compactor, several pharmaceutical powders were compressed into sheets or flakes, which then were reduced in size by an oscillating granulator to form compacted granules. Several properties (bulk density, drop density, repose angle, and flow rate) of the powders and compacted granules were determined and compared. The primary effect of the roller compactor was to increase the bulk density without a significant change in flowability. Two materials compacted at five pressures demonstrated that the bulk and drop density are linearly related to the logarithm of compaction pressure.

Keyphrases □ Powders—densification by concavo-convex roller compactor, effects on flowability □ Compacted granules—densification of powders by a concavo-convex roller compactor, effect on flowability □ Density—effects of a concavo-convex roller compactor

For many years, dry granulation by compression has been used to form granules of materials that are sensitive to moisture or heat. Dry granulation consists of compacting powder to form a slug with a heavy duty, rotary tablet press or a solid strip using a roller compactor and then reducing its size by milling or screening to achieve a desired granule. The advantages of the roller compactor over the tablet press slugging process include greater production capacity, more control over pressure and dwell time, and no need for lubrication of the powder (1). The powder is force fed by a variable-speed screw feeder to the nip of two counter-rotating rollers, which deaerate and compress the powder into a sheet or flake. The pressure may be varied by control of hydraulic cylinders, which apply the force to a roller. The pressure required varies with the material and the desired density of the granule. The roller compactor may be used for densification of powders for encapsulation, for making a granulation for direct tableting, and for producing a directly compressible excipient that can be blended with the active ingredients.

In the conventional flat roller compactor in which the angle of the inner wall slope of the rim is zero, an adequate supply of powder is not delivered to the gripping and compressing zone by the screw feeder because the stationary side seals act as a resistance to the powder flow. A rectangular aperture chute fitted at the end of the feed screw has been suggested to provide a more uniform supply of powder to the rollers; however, it does not prevent the compression pressure from being greater toward the middle of the width of the rollers than toward the edges (2).

This study demonstrated the usefulness of a concavo-convex roller compactor to increase the density of several pharmaceutical powders and measured some pharmaceutical characteristics of these compacted granules.

EXPERIMENTAL

Bulk Materials and Their Properties—The powders, purchased in bulk, were acetaminophen USP, aminobenzoic acid, precipitated calcium carbonate USP, dibasic calcium phosphate dihydrate USP, granular dicalcium phosphate[1], hydrous lactose[2], light magnesium carbonate USP, sulfadiazine USP, and sulfisoxazole USP. Each powder was transferred by a spatula into a 100-ml cylindrical graduate, and the volume and weight of the powder were determined. The bulk density is the quotient of the weight and volume. Each graduate containing the powder then was dropped five times from a height of 5 cm onto a wooden surface. The volume and weight of the powder were determined, and the quotient was defined as the drop density.

The repose angle was measured by placing the bulk powder in a funnel and allowing the powder to be discharged until the circumference of a circular dish with a radius r was just touched by the pile of powder formed (3). The height h of the pile was measured. The response angle ϕ is defined by $\phi = \tan^{-1} h/r$.

The flow rate in grams per second was determined in a flowmeter with a 1.905-cm circular orifice (4). The particle-size distribution was determined by a suitable nest of sieves in a sonic sifter[3]. For materials anticipated to be 200 mesh, a sedimentation technique was employed with an Andreasen pipet[4].

Compaction—The powder was compacted in a concavo-convex roller compactor[5] using grooved rollers. The pressure was adjusted and measured by means of a gauge incorporated into the hydraulic system of the compactor. The speeds of the feed screw and the rollers were adjusted for each powder so that compacted strips or flakes were produced and the current of the roller ammeter did not exceed 2 amp. The flakes and

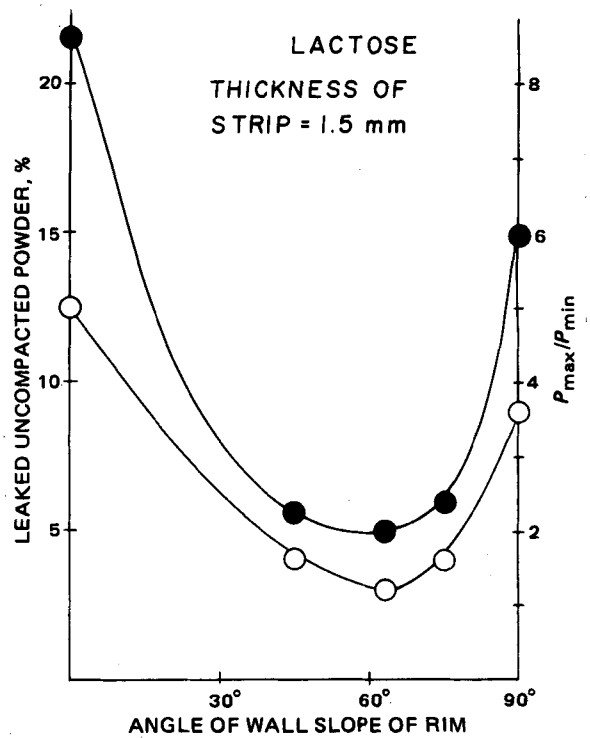

Figure 1—*Percent leakage and pressure distribution in relation to wall slope of rim. Key: ●, leakage; and ○, P_{max}/P_{min}. (Reproduced, with permission, from Ref. 2.)*

[1] Emcompress, Edward Mendell Co., Carmel, NY 10512.
[2] Spray dried, Foremost Foods Co., San Francisco, CA 44104.
[3] Allen-Bradley, Milwaukee, Wis.
[4] Fisher Scientific Co., Chicago, IL 60143.
[5] Freund Model Mini, Vector Corp., Marion, IA 52302.

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Table I—Pharmaceutical Properties of Selected Powders

Bulk Material	Bulk Density, g/cm³	Drop Density, g/cm³	Repose Angle	Flow Rate, g/sec	Median Size, μm
Acetaminophen	0.360	0.458	46.8°	Blocked	45[a]
Aminobenzoic acid	0.334	0.470	46.8°	Blocked	130[a]
Calcium carbonate, precipitated	0.267	0.322	41.6°	Blocked	23[a]
Dibasic calcium phosphate dihydrate	0.695	0.746	40.4°	Blocked	23[a]
Dicalcium phosphate, granular[b]	0.890	0.925	33.4°	66.8	160
Lactose, hydrous	0.633	0.774	31.9°	44.6	160
Magnesium carbonate, light	0.152	0.168	44.3°	Blocked	3[a]
Sulfadiazine	0.296	0.314	52.9°	Blocked	80[a]
Sulfisoxazole	0.368	0.430	51.5°	Blocked	70[a]

[a] Sedimentation by Andreasen pipet. [b] Emcompress.

Table II—Pharmaceutical Properties of Granules Compacted at 140 kg/cm² and Passed through 1-mm Screen in an Oscillating Granulator

Compacted Granules	Bulk Density, g/cm³	Drop Density, g/cm³	Repose Angle	Flow Rate, g/sec	Median Size, μm	Crushing Load[a], g
Acetaminophen	0.567	0.646	43.0°	Blocked	700	<15
Aminobenzoic acid	0.491	0.586	43.7°	Blocked	600	39.3 (13.3)[b]
Calcium carbonate, precipitated	0.657	0.835	38.7°	Blocked	680	34.6 (9.2)
Dibasic calcium phosphate dihydrate	0.943	1.215	44.3°	Blocked	580	29.9 (9.7)
Dicalcium phosphate, granular[c]	0.939	1.115	36.2°	Blocked	440	—
Lactose, hydrous	0.697	0.809	40.5°	Blocked	480	33.5 (15.4)
Magnesium carbonate, light	0.460	0.565	38.6°	Pulsating[d]	670	30.9 (9.0)
Sulfadiazine	0.592	0.712	41.6°	Pulsating[d]	730	80.0 (32.5)
Sulfisoxazole	0.610	0.735	40.2°	Blocked	730	40.1 (11.7)

[a] Average of 10 determinations on 18/20-mesh size fraction. [b] Standard deviation in parentheses. [c] Emcompress. [d] From 20.2 to 32.8 g/sec.

any uncompacted powder were separated using a 10-mesh sieve, and the finer material was returned to the hopper. The densified compact was processed by an oscillating granulator[6] fitted with a 1.0-mm screen. The physical properties of the resulting granules of the compact were measured as described previously.

Crushing Load—By means of sieves, a 18/20-mesh size fraction (920 μm ± 10%) of each compacted granule was collected. A viewing port was cut near the end of a 100-ml syringe from which the tip had been removed (5). A granule was placed on a flat metal platform, and the syringe was vertically fitted over it. A hollow plunger was gently lowered into the supporting syringe until its flat face contacted the granule. Mercury was dispensed at a given rate from a separator into the hollow plunger until the granule fractured. The crush load was the sum of the weight of the plunger and the mercury it contained.

RESULTS AND DISCUSSION

Within the past 5 years, a roller compactor with a concavo-convex roller pair, which maintains their mutual fit while rotating, has been marketed. In the design, the height of the rim and the slope of the inner wall determine the amount of powder to be gripped and compressed. The presence of the additional inner walls of the rims means a greater area of powder is in contact with the roller, and increased powder is subjected to the roller frictional drive in the region of the side seals. This feature counteracts the side seal effect. Thus, the proper selection of the rimmed roller design provides that: (*a*) an adequate supply of powder is delivered into the gripping and compression zone to form a compacted strip and (*b*) this powder is conveyed fully into the narrowest part of the roller gap, essentially eliminating the influence of the side seals.

Satisfying these two conditions may depend on the physical properties of the powder; however, in practice, an angle of 65° for the inner wall slope of the rims or flanges and a ridge height of 7 mm provide uniform compression pressure if proper adjustments are made in the operating conditions such as roller gap, speed of screw feed, and speed of rollers. The influence of the angle of the rim wall slope on the distribution of pressure across the width of the roller and the leakage of power is shown in Fig. 1. The ratio, P_{max}/P_{min}, of the maximal and minimal pressures across the width of the rollers represents a nonuniformity index.

By means of a concavo-convex roller pair similar to that shown in Fig. 2, eight compounds with a median diameter ranging from 3 to 160 μm

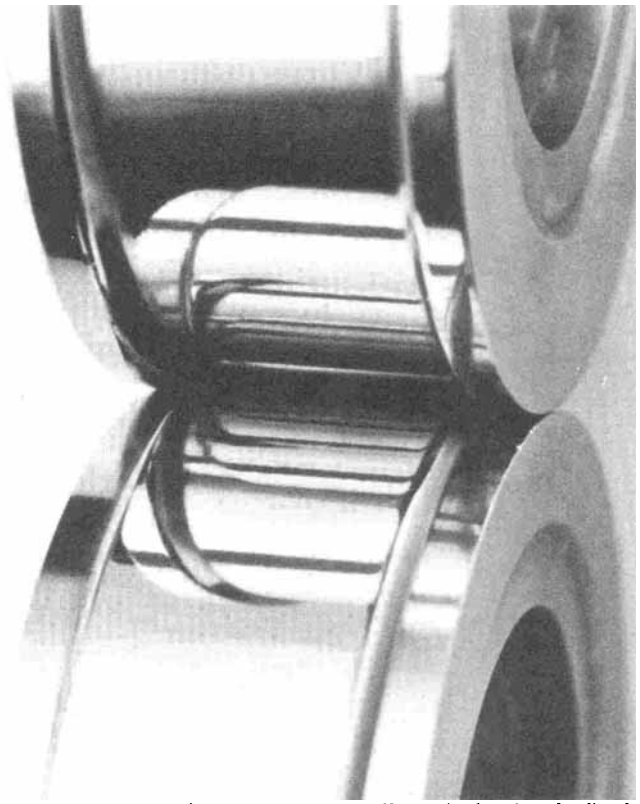

Figure 2—*A smooth concavo-convex roller pair showing the fit of the rollers and the wall slope of 65°.*

[6] Type FGS, Erweka-Apparatebau, GmbH, Heusenstamm Kr., Offenbach/Main, West Germany.

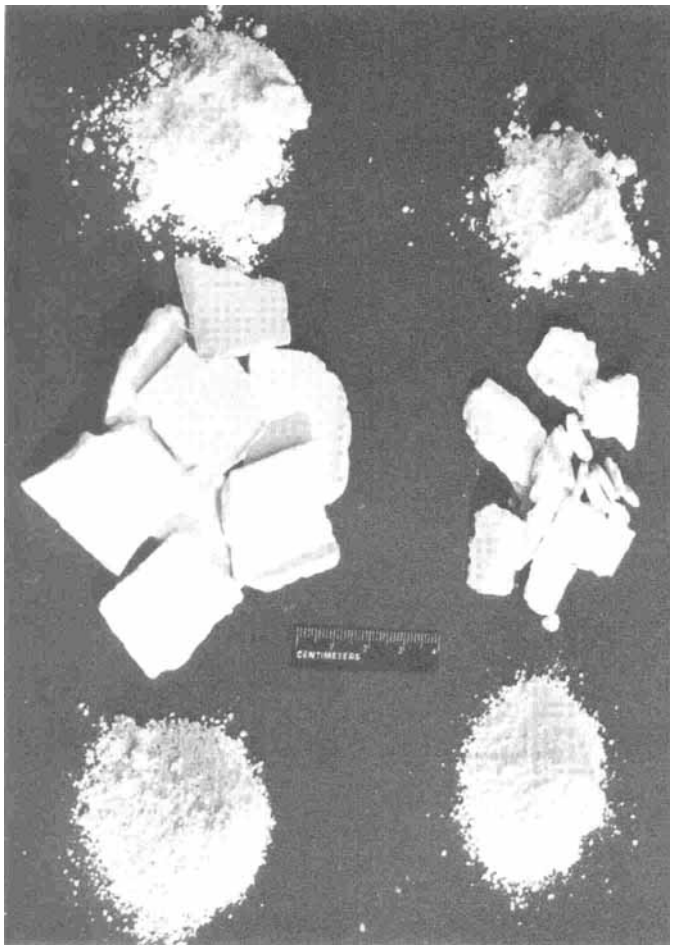

Figure 3—*Bulk and roller compacted materials. The upper piles are the bulk powders, the middle samples are the flakes of compacted materials, and the lower piles are the compacted granules prepared by passing the flakes through a 1.0-mm screen in an oscillating granulator. Aminobenzoic acid is on the left, and sulfadiazine is on the right.*

were compacted under a pressure of 140 kg/cm^2. The powders listed in Table I were compacted into sheets or flakes as shown in Fig. 3 for aminobenzoic acid and sulfadiazine.

Since the roller compactor is used to densify powders to be encapsulated or tableted, the sheets or flakes were reduced to a size common to these operations by means of an oscillating granulator fitted with a 1.0-mm screen. The median diameter of the compacted granule shown in Table II was determined by the 50% size read from a plot of the size against percent less than the stated size as determined experimentally by sieve analysis. A composite of these plots (Fig. 4) shows that the compacted granules (except lactose and dicalcium phosphate dihydrate) had a median diameter of ~700 μm. Lactose and dicalcium phosphate dihydrate were fragmented during compression (6, 7). The flakes of lactose and dicalcium phosphate dihydrate may have been fractured due to their brittle nature during processing in the oscillating granulator to produce a smaller median diameter than the other materials.

The crushing load or the weight in grams required to fracture a granule was determined (Table II). The crushing load for lactose granules prepared by roller compaction was 33.5 g. The crushing loads for lactose granules prepared by wet granulation were 33.9, 116, and 358.8 g for 1, 3, and 5%, respectively, of povidone as a binding agent (3). Although the

Table III—Comparison of Bulk Density, Drop Density, and Repose Angle of Powder and Compacted Granules

Material	Ratio of Bulk Density of Compacted Granule to Bulk Density of Powder	Ratio of Drop Density of Compacted Granule to Drop Density of Powder	Change in Repose Angle
Acetaminophen	1.57	1.41	−3.8°
Aminobenzoic acid	1.47	1.25	−3.1°
Calcium carbonate	2.46	2.59	−2.9°
Dibasic calcium phosphate dihydrate	1.35	1.63	+3.9°
Dicalcium phosphate, granular[a]	1.05	1.20	+2.8°
Lactose, hydrous	1.10	1.04	+8.6°
Magnesium carbonate	3.03	3.36	−5.7°
Sulfadiazine	2.00	2.27	−11.3°
Sulfisoxazole	1.66	1.71	−11.3°

[a] Emcompress.

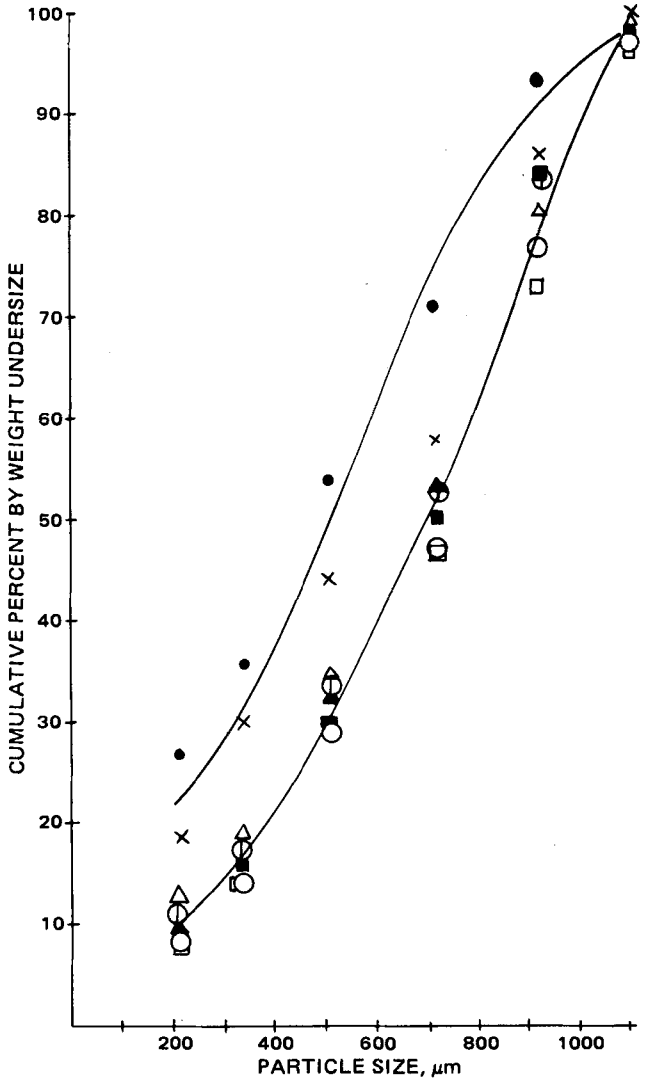

Figure 4—*Particle-size distribution of compacted granules. Key: ■, acetaminophen; Φ, aminobenzoic acid; △, calcium carbonate; ×, dibasic calcium phosphate; ●, lactose; ▲, magnesium carbonate; □, sulfadiazine; and ○, sulfisoxazole.*

Table IV—Effect of Compaction Pressure on Bulk Density

Pressure, kg/cm^2	Density, g/cm^3			
	Calcium Carbonate		Magnesium Carbonate	
	Bulk	Drop	Bulk	Drop
50	0.477	0.577	0.311	0.385
70	0.551	0.674	0.328	0.415
90	0.547	0.697	0.370	0.463
110	0.609	0.784	0.396	0.489
140	0.657	0.835	0.460	0.565

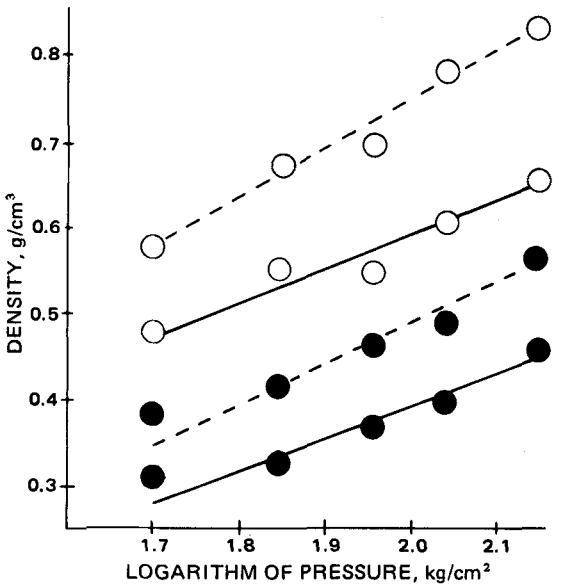

Figure 5—*Relationship of bulk and drop densities to logarithm of roller pressure. Key: ○, calcium carbonate; ●, magnesium carbonate; —, bulk density; and ---, drop density.*

crushing loads for lactose and dibasic calcium phosphate dihydrate were similar, the magnitude did not differ markedly from that of the materials. Thus, no correlation is apparent between the size of the material passed through the oscillating granulator and the crushing load of the compacted granules. In pharmaceutical processes, a property of a material is often influenced by the physicochemical nature of the material in addition to the process itself. Even more emphatically than the variation of the particle-size distribution, the effect of the nature of the material is demonstrated by phenacetin, which did not compact in the pressure range of 50–140 kg/cm^2.

As shown in Table III, the bulk density of the compacted granules was double to triple that of the bulk density of the powder for calcium carbonate, magnesium carbonate, and sulfadiazine. For acetaminophen, aminobenzoic acid, dibasic calcium phosphate dihydrate, and sulfisoxazole, the bulk density of the compacted granules was increased ~50% more than that of the bulk powder. Essentially the same relationship was demonstrated between the drop density of the compacted granules and that of the powder.

The primary effect of compaction was to increase the bulk density; little or no effect was shown on flowability. A decrease in the repose angle is intuitively associated with improved flowability. Although the repose angle for six materials was less after the materials were compacted, the compacted granules still possessed poor mobility. Only magnesium carbonate and sulfadiazine were discharged from the flowmeter, and their flow was a pulsating one. The repose angle increased for dibasic calcium phosphate dihydrate and hydrous lactose. For the hydrous lactose and granular dicalcium phosphate[1], which were marketed as readily flowable materials, the flow rate decreased from 44.6 and 66.8 g/sec, respectively, to a blockage in the flowmeter, indicating that compaction had destroyed the desired flowability.

Calcium carbonate and magnesium carbonate were selected to study the influence of compaction pressure on bulk density, because they had the smallest median diameters and lowest bulk densities. The bulk and drop densities of these materials compacted at five pressures are given in Table IV; clearly, the density increased as the compaction pressure increased. As shown in Fig. 5, there was a linear relationship between the bulk and drop density and the logarithm of compaction pressure.

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High-Pressure Liquid Chromatographic Determination of Chlorothiazide and Hydrochlorothiazide in Plasma and Urine: Preliminary Results of Clinical Studies

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Abstract □ High-pressure liquid chromatographic procedures were developed for the determination of chlorothiazide and hydrochlorothiazide in plasma and urine. The plasma assay incorporates a preextraction procedure that eliminates interference by endogenous substances. Chromatography is carried out on an octadecyl reversed-phase column. Mobile phases are 15% methanol in 0.01 *M* acetic acid for plasma and 4% acetonitrile in 0.01 *M* sodium perchlorate, adjusted to pH 4.6, for urine. At a flow rate of 2.5 ml/min, the retention times for chlorothiazide and hydrochlorothiazide are 3.5 and 4.6 min for plasma and 10.5 and 13.5 min for urine, respectively. Preliminary results of a clinical study in fasting male volunteers showed that the plasma levels and urinary excretion rate of chlorothiazide peaked at 1–2 hr following a 500-mg oral dose and subsequently declined irregularly. On the other hand, the plasma levels and urinary excretion rate of hydrochlorothiazide peaked at 2–3 hr following a 50-mg oral dose and subsequently declined in biphasic fashion. Urinary excretion rates of both chlorothiazide and hydrochlorothiazide closely resemble their concentration profiles in plasma.

Keyphrases □ Chlorothiazide—simultaneous high-pressure liquid chromatographic determinations with hydrochlorothiazide, plasma and urine □ Hydrochlorothiazide—simultaneous high-pressure liquid chromatographic determinations with chlorothiazide, plasma and urine □ High-pressure liquid chromatography—simultaneous determinations of chlorothiazide and hydrochlorothiazide, plasma and urine

Chlorothiazide and hydrochlorothiazide, two thiazide diuretics, are used commonly for treatment of hypertension, congestive heart failure, and other edematous conditions. The spectrophotometric methods originally used to measure these compounds in urine (1–4) are based on derivatizations involving the Bratton–Marshall reaction

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