

mulations could be correlated with the biological availability subsequently demonstrated in humans.

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\* To whom inquiries should be directed.

## Real Flow Measurements on Time-Dependent Thixotropic Fluids

ROGER L. SCHNAARE\*, RAFIQ M. SHEIKH\*, PAUL J. NIEBERGALL, and EDWIN T. SUGITA

**Abstract** □ An experimental procedure was developed in which shear stress *versus* time data at a constant shear rate are extrapolated to structural equilibrium conditions utilizing both the upcurve and the downcurve. This procedure allows the construction of a flow curve by plotting the equilibrium shear stress,  $F_e$ , *versus* the shear rate. Such an equilibrium flow curve is independent of all experimental conditions and of shear history and does not exhibit a hysteresis loop. The method also yields apparent rate constants for characterizing thixotropic behavior on an unequivocal basis. The extrapolation

procedure was developed using a cup and bob viscometer but is generally applicable to any continuous shear viscometer.

**Keyphrases** □ Thixotropic systems—equilibrium flow curve constructed from shear stress and shear rate data, apparent rate constants calculated □ Viscosity—thixotropic systems, equilibrium flow curve constructed, apparent rate constants calculated □ Shear stress and rate—thixotropic systems, data used in construction of equilibrium flow curve

A thixotropic material, as defined by Bauer and Collins (1), exhibits a "time-dependent, reversible and isothermal decrease of viscosity with shear in flow." This behavior is universally accepted as being indicative of an equilibrium process between the breakdown and buildup of structure as the material is subjected to shear (2-6). It follows that quantitative measurements of the viscosity or flow of such a system must be dependent on how close the system is to equilibrium. To be completely rigorous, a flow curve should be three dimensional, including time as the third variable (4) in addition to shear stress and shear rate.

#### BACKGROUND

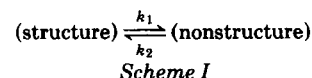
This time dependency is experimentally evident from the common observation that flow curves are highly dependent on experimental conditions, *i.e.*, the rate at which the shear rate is increased or decreased, the length of time a sample is subjected to any one rate of shear, how many times the flow curve is repeated, and the degree of agitation of the sample prior to measurement (7-9).

It is common practice to report flow data indicating as explicitly as possible the exact experimental conditions. This practice is based

on the assumption that variability can be eliminated by duplicating experimental conditions, allowing results to be compared on a relative, albeit arbitrary, basis. This assumption has not been found to be true in actual experience, and experimental data will be presented to illustrate this point.

The difficulty arises from the inability to duplicate the "shear history" of the sample and the uncertainty in the degree of structural equilibrium at a given shear rate. Other investigators simply admit that certain flow curves are not reproducible (2).

It is generally agreed (10, 11) that the structural state of such a material under shear can be represented by a first-order equilibrium process (Scheme I):



and that the shear stress is a function of structure such that, at equilibrium for a given shear rate:

$$\left[ \frac{d(\text{structure})}{dt} \right]_S \equiv \left[ \frac{dF}{dt} \right]_S = 0 \quad (\text{Eq. 1})$$

The correct procedure then for determining a time-dependent flow curve would be to indicate the point in time relative to the degree of structure at which shear stress measurements are made (4). The two simplest references points are at time  $t = 0$ , corresponding to the

maximum structural state of the material, and at  $t = \infty$  or at a time sufficiently great to ensure structural equilibrium.

Experimentally, the easiest parameter to measure is the shear stress at structural equilibrium by letting the material shear in a viscometer until no further change in stress is detected. This approach turns out to be impractical for most real time-dependent systems. Similarly, the direct determination of the shear at zero time is not possible because of instrument response and, most importantly, the effect of the sample's shear history on stress measurements.

The alternative procedure for determining  $F_0$  or  $F_e$  is to use extrapolation methods. Oldroyd (12) indicated that shear stress should decay exponentially at a constant shear rate from an initial stress value as:

$$F = F_0 e^{-kt} \quad (\text{Eq. 2})$$

The constant  $k$  is equivalent to  $1/t_r$ , where  $t_r$  is interpreted as a relaxation time. Equation 2, corresponding to the equilibrium process in Scheme I in which  $k_2 \gg k_1$ , would appear to be useful for determining  $F_0$  from extrapolation of initial stress data. The empirical, linear relationship between  $F$  and  $\log(t)$  observed by Weltman (13) appears to be valid under comparable conditions.

The equilibrium process has been considered (14), giving:

$$F = F_e + (F_0 - F_e)e^{-kt} \quad (\text{Eq. 3})$$

and it has been derived from thermodynamic and rheological principles by others (15-17). The predicted linear relationship between  $\ln(F - F_e)$  and  $t$  is found in practice, and it appears that  $F_e$  and  $F_0$  can be determined from shear stress data by usual numerical methods.

Unfortunately, these plotting procedures *do not* work in practice, because time,  $t$ , is not an absolute value as far as structure is concerned. In measuring a shear stress, the material at some point is transferred from a container to the viscometer, the instrument is turned on, and the time is noted as  $t = 0$ , the reference point denoting complete structure. However, the structure cannot be complete, since some shear must be introduced in transferring the sample.

It is possible in some cases to let the sample rest for a sufficiently long time to ensure complete structure. In that case,  $t = 0$  is determined on an absolute basis. Once the material is moved or sheared, it again becomes impossible to identify  $t = 0$  at any other shear rate. There is also the uncertainty as to whether, at successive shear rates,  $F_0$  refers to the structure at rest, the equilibrium structure at the preceding shear rate, or a unique structure associated with each shear rate.

The only readily available reference point in the rheogram is the equilibrium condition, and a convenient experimental method is suggested for obtaining the shear stress at structural equilibrium independent of shear history.

## EXPERIMENTAL

**Preparation of Samples**—The carbomer 940 dispersion was prepared by mixing the dry powder and distilled water with a mechanical stirrer for 1 hr. After standing for 30 min, potassium hydroxide solution was added to pH 7. Bentonite dispersions were prepared according to USP specifications.

**Rheological Measurements**—All measurements were made on a rotational cup and bob viscometer<sup>1</sup> at  $25 \pm 0.1^\circ$ . The viscometer has a speed range of 5-350 rpm, with the shear stress being measured at the bob surface. The dimensions of the various cups and bobs used are listed in Table I.

**Selection of Shear Rate**—For Newtonian fluids, shear rates were used as derived from the Margules equation (4). At the bob surface:

$$S = 2R_c^2\Omega/(R_c^2 - R_b^2) \quad (\text{Eq. 4})$$

or:

$$S = 0.2094 (\text{rpm}) R_c^2/(R_c^2 - R_b^2) = K_s (\text{rpm}) \quad (\text{Eq. 5})$$

The shear stress is determined by:

$$F = K_f (\text{dial readings}) \quad (\text{Eq. 6})$$

where the constant  $K_f$  is obtained from calibration of the viscometer

Table I—Dimensions and Constants for the Viscometer

Cup and Bob No-tation	$R_c$ , cm	$R_b$ , cm	$K_s$ (Eq. 5)	$K_f$ (Eq. 6)	$K_1$ (Eq. 7)	$K_2$ (Eq. 7)
A/A	2.360	2.223	1.969	1.887	0.0553	0.00100
A/B	2.360	1.556	0.3704	4.144	0.3613	0.03927
B/B	1.945	1.556	0.5817	4.136	0.2068	0.01338

with standard Newtonian oils and the shear rates as calculated by Eq. 5 for each cup and bob combination. Values for the constants  $K_s$  and  $K_f$  are listed in Table I.

If the shear rate and shear stress, as defined by Eqs. 5 and 6, are used to construct a flow curve for a time-independent non-Newtonian fluid, a separate curve results for each cup and bob combination. This experimental observation is illustrated by the upper three curves in Fig. 1. Obviously, one cannot describe the flow of a fluid with three distinct, separate curves.

Several approaches have been tried to overcome this lack of reproducibility. One approach is to use a shear rate derived on some basis thought to account for non-Newtonian behavior. Shangraw *et al.* (18) discussed several "non-Newtonian" shear rates. This approach has not eliminated the discrepancy, as depicted by the flow data for the carbomer in Fig. 1. In fact, a different flow curve will result for each shear rate using the same shear stress data obtained from a single fluid and a single cup and bob combination.

There are at least two published procedures for correcting the Newtonian shear rates as calculated by Eq. 5 for non-Newtonian behavior (19-21). The single bob procedure (19) is the most convenient and consistent.

The true non-Newtonian shear rate,  $S'$ , can be obtained from the Newtonian shear rate and the experimental data with:

$$S' = S[1 + K_1(1/n - 1) + K_2(1/n - 1)^2] \quad (\text{Eq. 7})$$

where:

$$K_1 = (R_c^2 - R_b^2)[1 + 2/3 \ln(R_c/R_b)]/2R_c^2 \quad (\text{Eq. 8})$$

$$K_2 = (R_c^2 - R_b^2)\ln(R_c/R_b)/6R_c^2 \quad (\text{Eq. 9})$$

and:

$$n = d(\ln F)/d(\ln S) \quad (\text{Eq. 10})$$

The two constants,  $K_1$  and  $K_2$ , are functions of the instrument, *i.e.*, independent of the fluid being measured. Values of  $K_1$  and  $K_2$  for the viscometer are listed in Table I. The term  $n$  is a function of the instrument and the fluid and must be determined experimentally from the flow data. Fortunately, a plot of  $\ln(F)$  versus  $\ln(S)$  for many non-Newtonian fluids is linear, so  $n$  is a constant for a particular fluid measured with a particular cup and bob combination. If  $d(\ln F)/d(\ln S)$  is not constant, an extended form of Eq. 7 must be used (see Ref. 22).

This correction procedure was applied to the three flow curves for the carbomer in Fig. 1. The resultant corrected flow curve, obtained

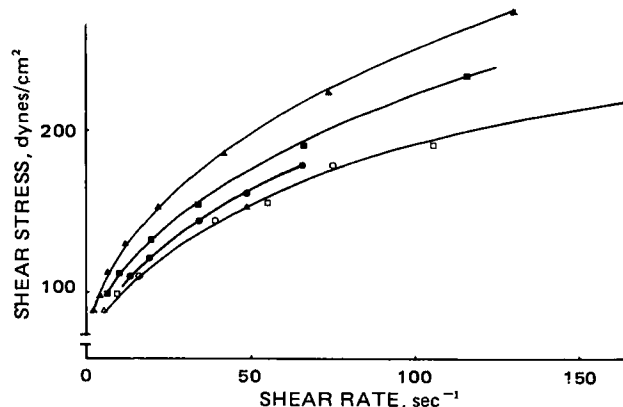
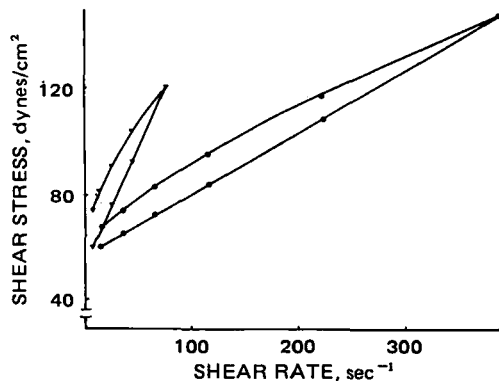


Figure 1—Time-independent flow curves for 0.1% carbomer 940 dispersion. Key:  $\Delta$ , measuring system A/B;  $\blacksquare$ , measuring system B/B;  $\bullet$ , measuring system A/A; and  $\Delta$ ,  $\square$ ,  $\circ$ , data corrected according to Eq. 7.

<sup>1</sup> Rheomat 15, Contraves Corp., Zurich, Switzerland.



**Figure 2**—Effect of the measuring system on the thixotropic flow curve of 7.0% bentonite dispersion. Key:  $\nabla$ , measuring system B/B; and  $\bullet$ , measuring system A/A. Shear interval = 5 min.

by plotting shear stress versus the corrected shear rate, is the true flow curve and is independent of the viscometer. It has been shown repeatedly (23) that viscosity data from widely differing types of viscometers, when properly corrected for non-Newtonian effects, result in a single flow curve for a given fluid. Such corrections must be applied to non-Newtonian flow data unless such corrections are shown to be insignificant.

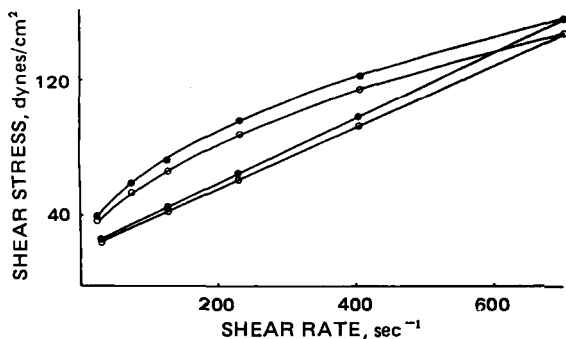
## RESULTS AND DISCUSSION

### Lack of Reproducibility in Measuring Thixotropic Fluids—

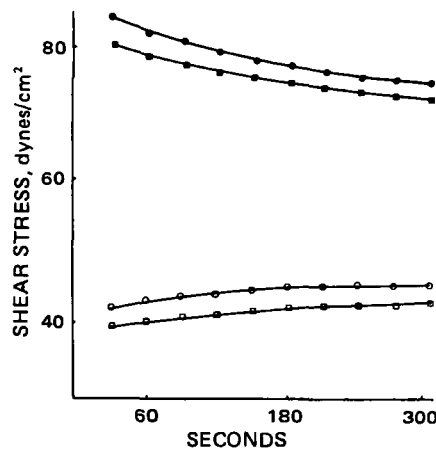
Figure 2 shows two flow curves for a bentonite dispersion, a typical thixotropic fluid. Two distinct hysteresis loops are observed for the same fluid measured with two different cup and bob combinations. This difference is not eliminated by applying a non-Newtonian correction to the shear rate. In addition, two loops were determined from the same fluid using the same cup and bob combination, but the time that the dispersion was sheared before switching to the next shear rate was varied (Fig. 3).

It is evident that, in addition to eliminating the instrument effect, one must eliminate the time-dependent effect, *i.e.*, one must measure shear stress at the same degree of structure or at the same reference point relative to structure. Figure 4 shows some shear stress data as a function of time. All four curves were measured at the same shear rate using the same fluid and the same cup and bob combination. The two upper curves were measured on the upcurve of the hysteresis loop, and the two lower curves were measured on the downcurve.

One can see that since the values of the shear stress at  $t = 0$  are not identical for the two upper curves, the degree of structure at the beginning of the measurement was not identical either. This general observation indicates that the shear history or prior treatment of a fluid makes it impossible to start a rheological measurement at the same structural reference point for a time-dependent fluid. The only other convenient structural reference point that can be used is the condition of structural equilibrium. Indeed, all four curves in Fig. 4 approach the same shear stress at equilibrium. For many time-dependent fluids, shearing until equilibrium is reached is not practical.



**Figure 3**—Effect of shear interval on the thixotropic flow curve of 5.0% bentonite dispersion (measuring system A/A). Key:  $\bullet$ , shear interval of 5 min; and  $\circ$ , shear interval of 10 min.



**Figure 4**—Shear stress as a function of time at a constant shear rate for 5.0% bentonite dispersion (measuring system A/A). Key:  $\bullet$ ,  $\blacksquare$ , data collected on the upcurve from two experiments; and  $\circ$ ,  $\square$ , data collected on the downcurve from two experiments. Shear rate = 116  $\text{sec}^{-1}$ .

**Extrapolation to Structural Equilibrium**—Following Swinbourne (24, 25), Eq. 3 can be written for a time  $t + \Delta$  as:

$$F_{t+\Delta} = F_e + (F_0 - F_e)e^{-(t+\Delta)k} \quad (\text{Eq. 11})$$

Rearrangement of Eqs. 3 and 11 gives:

$$F_t - F_e = (F_0 - F_e)e^{-kt} \quad (\text{Eq. 12})$$

and:

$$F_{t+\Delta} - F_e = (F_0 - F_e)e^{-k(t+\Delta)} \quad (\text{Eq. 13})$$

Dividing Eq. 12 by Eq. 13 and rearranging give:

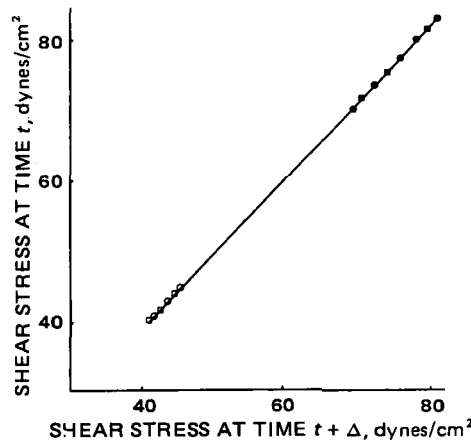
$$F_t = F_e(1 - e^{k\Delta}) + e^{k\Delta}F_{t+\Delta} \quad (\text{Eq. 14})$$

which predicts a linear relationship between the shear stress measured at time  $t$  and the shear stress measured at time  $t + \Delta$ . From this relationship, the equilibrium shear stress and the rate constant  $k$  can be obtained.

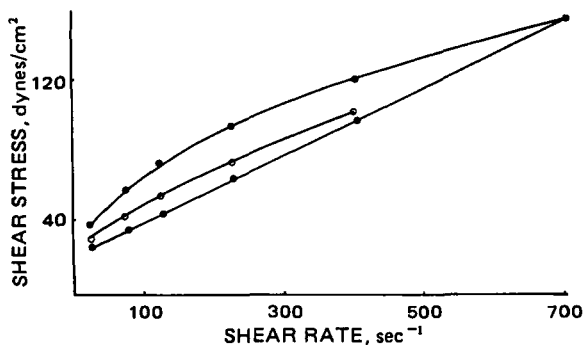
The predicted linear relationship is observed in Fig. 5, utilizing the data from all four curves in Fig. 4. Shear stress data from the upcurve as well as from the downcurve fall on the same line. In fact, since  $F_0$  and  $t$  have been eliminated in Eq. 14, shear stress data at a given shear rate can be collected in any manner; the only criterion is that the time interval,  $\Delta$ , be kept constant.

**Determination of True Equilibrium Flow Curve**—To determine such a flow curve using a cup and bob viscometer, the following steps are necessary:

1. Shear stress data are collected as a function of time at each shear rate (from both the upcurve and downcurve).



**Figure 5**—Swinbourne-type plot according to Eq. 12 for the data shown in Fig. 4.  $\Delta = 30$  sec.



**Figure 6**—Flow curve for 5.0% bentonite dispersion (measuring system A/A). Key: ●, data collected using a shear interval of 5 min; and ○, data extrapolated to equilibrium conditions.

2. The shear stress is extrapolated to equilibrium as indicated by Eq. 14.

3. The shear rate is corrected for non-Newtonian behavior according to Eq. 7.

4. The flow curve is constructed by plotting the equilibrium shear stress versus the corrected shear rate.

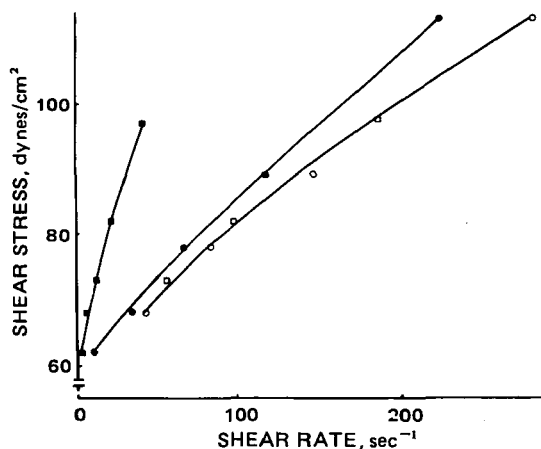
Figure 6 shows a typical hysteresis loop for a bentonite dispersion and the corresponding equilibrium flow curve obtained by plotting the equilibrium shear stress versus the uncorrected or Newtonian shear rates. The equilibrium curve lies within the loop as one would expect if the upcurve corresponds to structure breakdown and the downcurve to structure buildup.

The true equilibrium flow curve is shown in Fig. 7, where the non-Newtonian correction was applied to two equilibrium flow curves extrapolated from data for two different cup and bob combinations.

**Experimental Verification of Equilibrium**—The data in Table II are offered as experimental verification of the extrapolation procedure. The predicted equilibrium shear stress values were extrapolated from shear stress versus time data collected over a 10-min period using a time interval of  $\Delta = 30$  sec. The experimental values were obtained by shearing the dispersion at a constant rate for 10 hr, taking precautions to prevent evaporation of the solvent. The predicted and experimental values agree to within a 95% confidence limit.

## SUMMARY AND CONCLUSIONS

A convenient and rapid method for obtaining the true equilibrium flow curve for non-Newtonian time-dependent fluids was developed. The method is illustrated for a cup and bob viscometer but is applicable in principle for any continuous shear viscometer. The flow curve obtained is independent of the instrument used and the shear history of the sample, enabling rheological parameters to be compared on an absolute basis.



**Figure 7**—Equilibrium flow curves for 7.0% bentonite dispersion. Key: ■, measuring system A/B; ●, measuring system A/A; and □, O, data corrected according to Eq. 7.

**Table II**—Experimental versus Predicted Equilibrium Shear Stress for Bentonite Dispersions

Predicted (10 min)	Experimental (10 hr)
Bentonite, 5.0% <sup>a</sup>	
30.3	31.8
34.4	35.6
41.4	40.3
52.0	49.6
69.5	66.3
98.3	95.7
Bentonite, 8.0% <sup>b</sup>	
116	118
129	129

<sup>a</sup> Cup and bob A/A. <sup>b</sup> B/B.

As a consequence of the method, the hysteresis loop is not encountered. The loop as a measurement of thixotropic behavior has not shown much application anyway. The rate constant  $k$  in Eq. 14 is proposed as a more meaningful measure of thixotropy; its utility is currently being investigated.

## LIST OF SYMBOLS

- $k_1$  and  $k_2$  = first-order rate constants
- $t$  = time
- $F$  = shear stress
- $F_0$  = shear stress at zero time, *i.e.*, the shear stress corresponding to maximum structure
- $F_e$  = shear stress at structural equilibrium
- $S$  = Newtonian shear rate
- $S'$  = non-Newtonian shear rate
- $R_c$  and  $R_b$  = radius of the viscometer cup and bob, respectively
- $\Omega$  = angular velocity
- $K_s$  = constant relating shear rate with the rotational speed of the viscometer bob
- $K_f$  = constant relating shear stress to the viscometer dial reading
- $K_1$  and  $K_2$  = constants
- $n$  = slope of a  $\ln(F)$  versus  $\ln(S)$  plot
- $\Delta$  = time interval

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\* Currently a candidate for the Ph.D. degree at the Philadelphia College of Pharmacy and Science.

\* To whom inquiries should be directed.

## NOTES

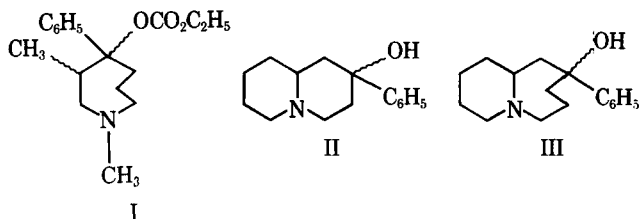
# Epimeric 5-Hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes

N. ABOL-ENEIN and J. SAM \*

**Abstract** □ The preparation of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes is described. One propionate ester exhibited weak analgesic activity.

**Keyphrases** □ Undecanes, substituted cyclic—epimers synthesized, analgesic activity evaluated □ 5-Hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes epimers—synthesized, analgesic activity evaluated □ Analgesic agents, potential—epimers of 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes synthesized and screened

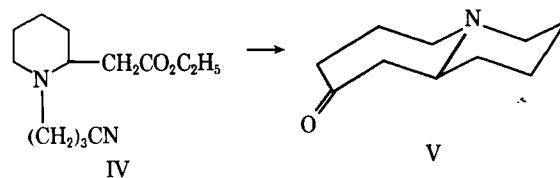
The potent analgesic activity exhibited by proheptazine (I) (1) and the esters of 2-hydroxy-2-phenylquinolizidines (II) (2) led to the investigation of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes (III) and the corresponding propionate esters. The preparation and stereochemistry of 6-hydroxy-6-aryl-1-azabicyclo[5.4.0]undecanes and their structural relationship to biologically active phenethylamines and analgesic piperidines were reported previously (3).



#### DISCUSSION

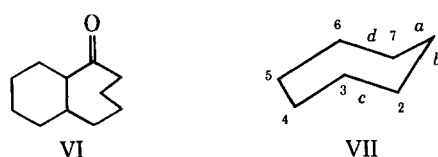
For the synthesis of III, 1-azabicyclo[5.4.0]undecan-5-one (V) was utilized. The procedure followed (Scheme I) for the preparation of V from ethyl 1-(3-cyanopropyl)piperidyl-2-acetate (IV) was similar to the method described (4) for the synthesis of 1-oxoquinolizidine.

Published reports (3-9) describing the stereochemical structure of bicyclo[5.4.0]undecan-2-one (VI), II, and related quinolizidines



Scheme I

were utilized in determining the stereochemical nature of the ring in V. The IR spectra of V is consistent with published data (2-9) on *trans*-fused II and related *trans*-fused ring systems. Since TLC indicated the formation of only one isomer, *trans*-fused Structure V was assigned to the product.



The reaction of phenylmagnesium bromide with V provided an 8:1 mixture of epimeric 5-hydroxy-5-phenyl-1-azabicyclo[5.4.0]undecanes (IIIa and IIIb). Because of the lack of definitive information on the conformation of heterocyclic ring systems containing more than five carbons (10, 11) and the high flexibility of seven-membered rings (12), a conclusive delineation of the conformation of IIIa and IIIb could not be determined. Investigators noted previously (13-16) that the stable conformation of cycloheptane is in a deformed chair position (VII). Moreover, the cyclohexane chair can be fused at any one of the four bonds marked a, b, c, and d without affecting the original conformation. Structures resulting from *trans*-fusion of the cyclohexane chair at a or b are readily interconvertible by a slight manipulation of C-4 and are the most favored, while the other two structures fused at c or d are quite rigid (5, 16).

The IR spectra of both IIIa and IIIb are similar in the hydroxyl absorption region (both show absorption at 3300  $\text{cm}^{-1}$  in carbon tetrachloride even on high dilutions) and in the aromatic region between 600 and 800  $\text{cm}^{-1}$ . Bohlmann bands do not appear in the spectrum of IIIa; the spectrum of IIIb includes bands at 2765, 2795, and 2860  $\text{cm}^{-1}$ , indicative of a *trans*-fused system. Sircar and Meyers