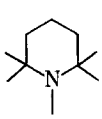
Aryl-2-piperidylcarbinols: Potential Cardiovascular Agents

JOSEPH SAM, DOROTHY NOBLES VACIK, and M. N. ABOUL-ENEIN

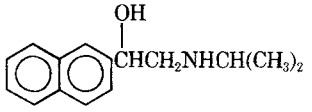
Abstract □ The syntheses of some substituted aryl-2-piperidylcarbinols are described. Weak α- and/or β-agonist and/or antagonist activity was observed in preliminary experimental studies in animals.

Keyphrases □ Aryl-2-piperidylcarbinols, substituted—synthesis, pharmacological screening □ Cardiovascular agents, potential—synthesis, pharmacological screening, aryl-2-piperidylcarbinols

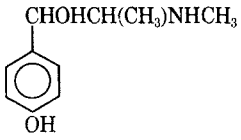
The presence of a hydrogenated benzyl piperidine system in the veratrum alkaloids (1), the hypotensive properties exhibited by some piperidine derivatives (2–6) (*e.g.*, pempidine, I), and the cardiovascular effects (7, 8) elicited by arylhydroxyalkylamines (*e.g.*, propranolol, II; and suprifen, III) prompted the investigation of some aryl-2-piperidylcarbinols (X, Table I).



I

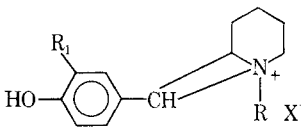


II

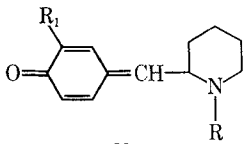


III

As the work progressed, it was anticipated that the structural characteristics of the phenyl-2-piperidylcarbinols would provide useful information regarding α- and β-agonist activity (9). Since intramolecular cyclization to the aziridine (IV) is sterically hindered, the quinone methide (V) probably would be a favored intermediate and consequently elicit β-agonist activity (9).

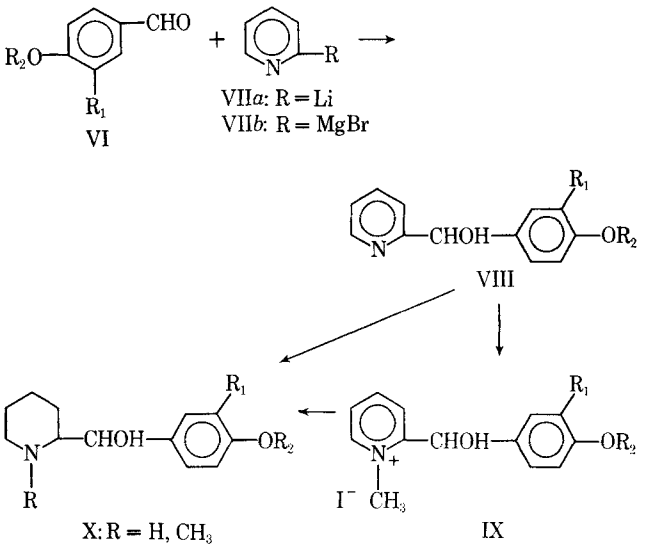


IV



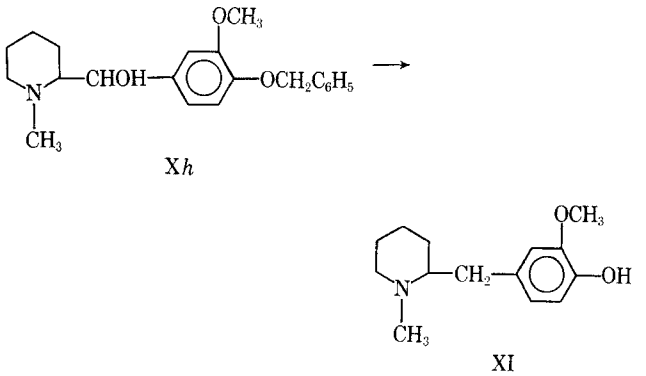
V

The preparation of aryl-2-pyridylcarbinols (VIII, Table II) was accomplished by the reaction of the appropriate benzaldehyde (VI) with either pyridyllithium (VII*a*) or pyridylmagnesium bromide (VII*b*) (Scheme I). The reaction of *p*-hydroxybenzaldehydes with an excess of the organometallic derivative provided approximately 10% yields of VIII (R_2 = H). The yields, although still low, were improved considerably by masking the phenols as the benzyl ethers. The hydrogenation of VIII or the methiodides (IX) provided the corresponding aryl-2-piperidylcarbinols (X).



Scheme I

The hydrogenolysis of 1-methyl-α-[(3-methoxy-4-benzyloxy)phenyl]-2-piperidylcarbinol hydriodide (X*h*) proceeded smoothly; however, hydrogen in excess of the amount necessary for debenzylation was consumed (Scheme II). This was not surprising inasmuch as benzyl



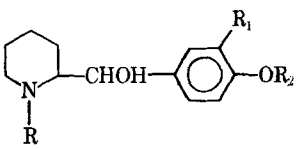
Scheme II

alcohols are known to undergo hydrogenolysis (10), especially under acidic conditions. The product was identified as the dehydrated and reduced compound, XI, *via* methylation to the dimethoxy derivative (XIV). The latter also was prepared by an alternate route from VIII*e* (Scheme III). Compound XIV from both synthetic routes was converted to the methiodide.

PHARMACOLOGY

Preliminary pharmacological data on the aryl-2-piperidylcarbinols (X) are summarized in Table III. None of the compounds showed significant adrenergic agonist activity relative to either the α- or β-receptor. The piperidines (X*a*–X*c*) without the *N*-methyl substituent exhibited very weak β-receptor blockade. In general, the

Table I—Aryl-2-piperidylcarbinols



Number[a]	R	R_1	R_2	Method	Recrystallization Solvent[b]	Melting Point	Yield, %	Molecular Formula	Analysis—Calcd.	Analysis—Found
X*a*	H	H	H	D	E	229–230°	50	$C_{12}H_{18}NO_2Cl$[c]	C, 59.14 H, 7.44 N, 5.75	C, 59.42 H, 7.53 N, 5.60
X*b*	H	OCH_3	H	D	E	250–251°	75	$C_{13}H_{20}NO_3Cl$[c]	C, 57.01 H, 7.36 N, 5.11	C, 57.16 H, 7.46 N, 4.92
X*c*	H	OCH_3	CH_3	D	E	201–202°	76	$C_{14}H_{22}NO_3Cl$[c]	C, 58.43 H, 7.70 N, 4.87	C, 58.46 H, 7.80 N, 4.68
X*d*	CH_3	H	H	E	M–Et	171–172°	52	$C_{13}H_{19}NO_2$	C, 70.56 H, 8.65 N, 6.33	C, 70.29 H, 8.71 N, 6.27
X*e*	CH_3	OCH_3	H	D	E–PE	163–164°	91	$C_{14}H_{21}NO_3$	C, 66.91 H, 8.42 N, 5.57	C, 66.81 H, 8.57 N, 5.33
X*f*	CH_3	OCH_3	CH_3	D		160–162°(0.15)[d]	70	$C_{15}H_{23}NO_3$	C, 67.90 H, 8.74 N, 5.28	C, 67.54 H, 8.85 N, 5.12
X*g*	CH_3	H	$CH_2C_6H_5$	D	E–Et	166–168°	63	$C_{20}H_{26}NO_2I$[e]	C, 54.66 H, 5.97 N, 3.19	C, 54.37 H, 6.07 N, 3.12
X*h*	CH_3	OCH_3	$CH_2C_6H_5$	D	W	207–210°	30	$C_{22}H_{27}NO_3I$[e]	C, 53.86 H, 5.83 N, 2.99	C, 53.66 H, 6.11 N, 2.95

[a] IR spectra are consistent with the assigned structures. [b] E = ethanol, Et = ether, M = methanol, PE = petroleum ether (30–60°), and W = water. [c] Hydrochloride. [d] Boiling point. [e] Hydriodide.

compounds were nonspecific, smooth muscle depressants of very low potency.

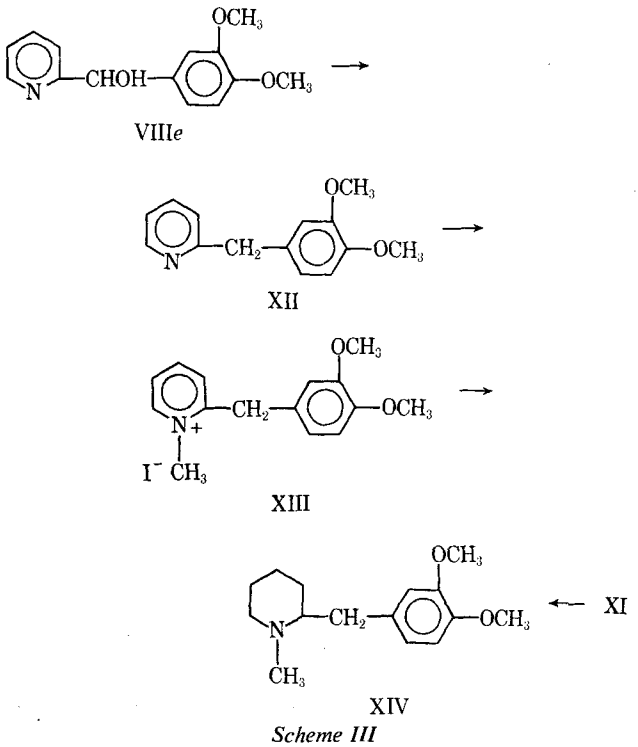
EXPERIMENTAL[1]

The procedures described by Buu-Hoi *et al.* (11) and Anker *et al.* (12) were utilized for the preparation of *p*-benzyloxybenzaldehyde and benzyloxyvanillin, respectively. Materials other than those described in the *Experimental* section were obtained from commercial sources.

Aryl-2-pyridylcarbinols (VIII, Table II)—*Method A*—Modification of the procedure of Wibaut *et al.* (13) was employed for the preparation of 2-pyridyllithium. A stirred, oxygen-free mixture of 100 ml. of anhydrous ether and 3.78 g. (0.4 mole) of lithium wire [flattened and cut into pieces approximately 0.64 cm. (0.25 in.) long], maintained at −10°, was treated dropwise with 27.4 g. (0.2 mole) of *n*-butyl bromide. The solution was stirred until the lithium disappeared; it was then cooled to −45° and maintained at this temperature while being treated dropwise with a solution of 31.6 g. (0.2 mole) of 2-bromopyridine in 80 ml. of anhydrous ether. The blood-red solution was stirred an additional hour and then treated slowly at −45° with a solution of 0.1 mole of the appropriate benzaldehyde in 100 ml. of anhydrous ether. The milky reaction mixture was stirred for an additional hour, allowed to come to room temperature, and then decomposed with cold 16% ammonium chloride. An ether or a methylene chloride extract of the mixture was dried over anhydrous sodium sulfate and evaporated. The residual material either was recrystallized or distilled.

Method B—A solution of 2-pyridylmagnesium bromide [prepared from 16 g. (0.1 mole) of 2-bromopyridine by the procedure described by Overhoff and Proost (14)] in 120 ml. of anhydrous ether was treated dropwise at 36° with a solution of 0.06 mole of the appropriate benzaldehyde in 50 ml. of anhydrous ether and thereafter stirred for 12 hr. at room temperature. The product was isolated as described under *Method A*.

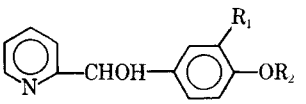
Method C—A solution of 0.016 mole of the benzyloxy derivative (VIII*a* and VIII*c*) in 230 ml. of methanol was hydrogenated in the presence of 0.6 g. of 10% palladium-on-charcoal for 28–30 hr. at room temperature at an initial hydrogen pressure of 48 p.s.i. The mixture was filtered, and the filtrate was evaporated under reduced pressure; the residual material was either recrystallized or converted to the hydrohalides or the methiodides in the usual manner and recrystallized.



Scheme III

[1] All melting points were taken on a Fisher-Johns melting-point apparatus and are corrected. IR data were obtained on all compounds with Perkin-Elmer model 137G and 257 IR spectrophotometers using KBr pellets or chloroform solutions.

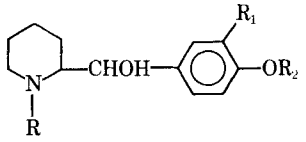
Table II—Aryl-2-pyridylcarbinols



Number[a]	R_1	R_2	Method	Recrystallization Solvent[b]	Melting Point	Yield, %	Molecular Formula	Analysis—Calcd.	Analysis—Found
VIII*a*	H	$CH_2C_6H_5$	B	A–Et	179–180°[c]	48	$C_{20}H_{20}NO_2I$[d]	C, 55.44 H, 4.63 N, 3.23	C, 55.54 H, 4.49 N, 3.36
VIII*b*	H	H	A,C	W	139–140°[e]	11,80	$C_{12}H_{11}NO_2$	C, 71.62 H, 5.50 N, 6.96	C, 71.14 H, 5.52 N, 7.12
VIII*c*	OCH_3	$CH_2C_6H_5$	A,B	E	156–158°[f]	43,40	$C_{21}H_{22}NO_3I$[d]	C, 54.44 H, 4.79 N, 3.02	C, 54.52 H, 4.85 N, 3.16
VIII*d*	OCH_3	H	A,C	A–M	171–172°[g,h]	10,90	$C_{13}H_{14}NO_3Cl$[i]	C, 58.35 H, 5.31 N, 5.24	C, 58.37 H, 5.30 N, 5.01
VIII*e*	OCH_3	CH_3	A,B	E–PE	93–94°[j,k,l]				

[a] IR spectra are in agreement with the assigned structures. [b] A = acetone, E = ethanol, EA = ethyl acetate, Et = ether, M = methanol, PE = petroleum ether (30–60°), and W = water. [c] Free base, m.p. 95–96° (E–Et). [d] Methiodide. [e] Hydrochloride, m.p. 174–175° (M–EA). [f] Free base, m.p. 124–125° (E). [g] The base was obtained as a yellow viscous oil. [h] The methiodide was obtained as a syrupy viscous oil. [i] Hydrochloride. [j] *Reference 15.* [k] Hydrochloride, m.p. 161–162° (M–EA). [l] Methiodide, m.p. 180–181° (E–W).

Table III—Adrenergic Activity



Number	R	R_1	R_2	β-Adrenergic Blockade[a,b]	β-Adrenergic Stimulation[a,c]	α-Adrenergic Blockade[d,e]	α-Adrenergic Blockade[d,f]	α-Adrenergic Stimulation[d,g]
X*a*	H	H	H	*ca.* 100	>1000	220	520	>1000
X*b*	H	OCH_3	H	320	>1000	310	820	>1000
X*c*	H	OCH_3	CH_3	52	>250	355	>1000	>1000
X*d*	CH_3	H	H	>1000	>1000	225	690	>1000
X*e*	CH_3	OCH_3	H	>1000	>1000	340	450	>1000
X*f*	CH_3	OCH_3	CH_3	>1000	>1000	130	450	>1000

[a] On guinea pig trachea. [b] Concentration (micrograms per milliliter) causing 50% inhibition of the relaxant action of isoproterenol. [c] Concentration (micrograms per milliliter) relaxing spontaneous tissue tonus by 75% of maximum. [d] On isolated rat seminal vesicle. [e] Concentration (micrograms per milliliter) causing 50% inhibition of norepinephrine. [f] Concentration (micrograms per milliliter) causing 50% inhibition of barium chloride. [g] Concentration (micrograms per milliliter) eliciting a contractile response 50% of the magnitude of epinephrine.

Aryl-2-piperidylcarbinols (X, Table I)—*Method D*—A solution or suspension of 0.032 mole of the hydrochloride or methiodide of the appropriate 2-pyridyl carbinol (VIII) in 150 ml. of water was hydrogenated in the presence of 0.5 g. of PtO_2 for 24–30 hr. at room temperature at an initial hydrogen pressure of 48 p.s.i. The mixture was filtered, and the filtrate was evaporated to dryness. The residual material was either recrystallized to yield the hydrohalide or treated with 10% sodium bicarbonate and concentrated ammonium hydroxide to pH 8, saturated with sodium chloride, and extracted with methylene chloride. The solvent was evaporated, and the residual amine was either recrystallized or distilled.

Method E—A solution of 0.04 mole of the appropriate 1-methyl-α-(4-benzyloxyphenyl)-2-piperidylcarbinol in 200 ml. of methanol was debenzylated as described under *Method C*.

2-(3,4-Dimethoxybenzyl)-1-methylpiperidine (XIV)—*Method F*—A solution of 6.9 g. (0.03 mole) of 2-(3,4-dimethoxybenzyl)pyridine (XII), prepared according to the method of Sugimoto (15), and 20 g. (0.14 mole) of methyl iodide in 100 ml. of acetonitrile was refluxed for 24 hr. The solvent was removed under reduced pressure. The residual crude methiodide (12.8 g.) was dissolved in 60 ml. of water and hydrogenated in the presence of 0.3 g. of platinum oxide at room temperature for 24–30 hr. at an initial hydrogen pressure of 48 p.s.i. The mixture was filtered and the filtrate treated with excess 10% sodium hydroxide. A chloroform extract (3 × 30 ml.) of the mixture was dried over anhydrous sodium sulfate and distilled at 126–130° (0.15 mm.) to give 4.6 g. (61%) of product. A picrate was prepared in the usual manner and recrystallized from ethanol–acetone; m.p. 150–151°.

Anal.—Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.72; H, 5.48; N, 11.71 Found: C, 52.70; H, 5.45; N, 12.02.

A methiodide was prepared in the usual manner and recrystallized from ethanol; m.p. 164–165°.

Anal.—Calcd. for $C_{16}H_{26}NO_2I$: C, 49.08; H, 6.69; N, 3.58. Found: C, 48.54; H, 6.54; N, 3.49.

Method G—The methylation procedure described by Vogel (16) was followed using 2 g. (0.008 mole) of 2-(4-hydroxy-3-methoxybenzyl)-1-methylpiperidine (XI), 1 g. (0.005 mole) of sodium hydroxide, 20 ml. of water, and 1.3 g. (0.01 mole) of dimethyl sulfate. The mixture was refluxed for 2 hr. with stirring and then treated with 25 ml. of water. An ether extract of the oil was washed with water and then dried over anhydrous sodium sulfate. Evaporation of the ether left an oil, which was converted to a picrate in the usual manner and recrystallized from ethanol; m.p. 149–150°. A mixture melting point with the product obtained from *Method F* showed no depression. IR spectra were identical.

2-(4-Hydroxy-3-methoxybenzyl)-1-methylpiperidine (XI)—A solution of 13.6 g. (0.04 mole) of 1-methyl-α-(3-methoxy-4-benzyloxyphenyl)-2-piperidylcarbinol hydriodide (X*h*) in 50 ml. of methanol was hydrogenated as described under *Method C*. The hydrochloride was prepared in the usual manner and was recrystallized from acetone–methanol to yield 4.5 g. (25%) of product; m.p. 220–221°.

Anal.—Calcd. for $C_{14}H_{22}NO_2Cl$: C, 61.87; H, 8.19; N, 5.15; Cl, 13.05. Found: C, 62.18; H, 7.58; N, 4.98; Cl, 12.95.

REFERENCES

(1) K. J. Morgan and J. A. Baltrop, *Quart. Rev.*, **12,** 36(1958).

(2) A. Spinks and E. H. P. Young, *Nature*, **181,** 1397(1958).

(3) L. Bretherick, G. E. Lee, E. Hunt, W. R. Wragg, and N. D. Edge, *ibid.*, **184,** 1707(1959).

(4) G. E. Lee, W. R. Wragg, S. J. Corne, N. D. Edge, and H. W. Reading, *ibid.*, **181**, 1717(1958).
(5) W. B. Lutz, S. Lazarus, and R. I. Meltzer, *J. Org. Chem.*, **27**, 1695(1962).
(6) J. E. Robertson, J. H. Biel, and R. DiPierro, *J. Med. Chem.*, **6**, 381(1963).
(7) Symposium on Beta Adrenergic Receptor Blockade, *Amer. J. Cardiol.*, **18**, 303(1966).
(8) T. Budesinsky and M. Protiva, "Synthetische Arzneimittel," Akademie Verlag, Berlin, Germany, 1961, p. 23.
(9) A. A. Larsen, *Nature*, **224**, 25(1969).
(10) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp. 81, 135.
(11) N. P. Buu-Hoi, M. Welsch, G. DeChamps, H. LeBihan, F. Binon, and N. D. Xuong, *J. Org. Chem.*, **18**, 121(1953).
(12) R. M. Anker, A. H. Cook, and I. M. Heilborn, *J. Chem. Soc.*, **1945**, 917.
(13) J. P. Wibaut, A. D. Johge, H. G. P. Voort, and P. P. L. Otto, *Rec. Trav. Chim.*, **70**, 1054(1951).
(14) J. Overhoff and W. Proost, *ibid.*, **57**, 184(1938).
(15) N. Sugimoto, *J. Pharm. Soc. Japan*, **76**, 1045(1956); through *Chem. Abstr.*, **51**, 3598(1957).
(16) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Wiley, New York, N. Y., 1956, p. 199.

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Stability of Salicylic Acid and Cetrimide System in the Presence of Additives

LUCY S. C. WAN

Abstract □ Various additives were added to the gel-like product which results from the interaction of salicylic acid with cetrimide. The additives were alcohols, acetone, water, glycerin, propylene glycol, polyethylene glycols, amyl acetate, heptane, hexadecane, dioxane, cyclohexane, benzene, methylbenzene, ethylbenzene, nitrobenzene, pyridine, tetralin, carbon tetrachloride, chloroform, liquefied phenol BP, and cresol BP. The first 10 compounds reduced the viscosity of the gel-like product to varying degrees, and the reduction generally increased with an increasing volume of the additive. The remaining 11 compounds together with the higher alcohols, from hexyl to decyl alcohol, increased the viscosity initially, followed soon after by a viscosity decrease. The instability of the system in the presence of the additives was probably due largely to their effect on the links in the network structure of the macromolecules which formed the gel-like product. The initial rise in viscosity could be due to a tendency of a small amount of the additive to bring the macromolecules closer together, thus making the system more viscous. The fall after this rise could be attributed to the breakup of the mesh with larger amounts of the additive and possibly to a change in the nature of the system.

Keyphrases □ Salicylic acid–cetrimide system—stability in presence of additives □ Cetrimide–salicylic acid interaction, stability—effect of additives □ Additives—effect on stability of salicylic acid–cetrimide system □ Viscosity—effect of additives on salicylic acid–cetrimide interaction

In previous papers (1–3), salicylic acid and its salts were found to interact with the quaternary ammonium type of surfactants in aqueous solutions, resulting in a marked increase in viscosity of the system. This viscosity was further enhanced when salts were added (2). The present report concerns the stability of the gel-like product in the presence of various compounds, many of which are commonly used as solvents. The study was undertaken to eliminate or break down the gel-like structure so as to gain an insight into the mechanism of the interaction. The results would be helpful in the investigation of the possible uses of the product.

EXPERIMENTAL

Materials—Salicylic acid was recrystallized, m.p. 158.5–159°. Cetrimide BP[1], which consisted chiefly of tetramethylammonium bromide, was used as supplied. The additives used were as follows: redistilled alcohols (methyl, ethyl, *n*-propyl, and *n*-butyl)[2], amyl alcohol[3], *n*-hexyl alcohol[3], *n*-heptyl alcohol[3], *n*-octyl alcohol[3], *n*-decyl alcohol[3], acetone[2], distilled water, glycerin BP, propylene glycol[3], polyethylene glycol 400 and 600[4], amyl acetate[3], heptane[3], hexadecane[3], dioxane[5], cyclohexane[3], benzene[3], methylbenzene[6], ethylbenzene[6], nitrobenzene[3], pyridine[7], tetralin[3], carbon tetrachloride[3], chloroform[8], liquefied phenol BP, and cresol BP.

Apparatus—A portable Ferranti viscometer[9] was used.

Measurement of Viscosity at 25°—Preliminary experiments had shown that generally the viscosity and rheological behavior of the systems produced by dissolving various amounts of salicylic acid in different concentrations of cetrimide were of the same pattern. A system containing 1.4% of the acid and 5% of the surfactant was chosen; on incorporation of additives, it would give viscosity values well within the measuring range of the viscometer. The gel-like product was formed by adding the required amount of salicylic acid to the cetrimide solution and was allowed to rotate in a thermostatically controlled water bath at 25 ± 0.5° until the acid went into solution. A sample of 50 g. (about 51 ml.) of the gel-like product so formed was equilibrated at the same temperature in a thermostatically controlled water bath, and the viscosity was determined at shear rates ranging from 78.56 to 234.6 $sec.^{-1}$.

One-tenth of a milliliter of the additive was added from a graduated pipet and mixed well, without removing the sample from the

[1] Glovers (Chemicals) Ltd., Leeds, England.
[2] Shell Company Ltd.
[3] British Drug House, Ltd., Poole, England.
[4] L. Light and Co., Colnbrook, England.
[5] May and Baker, Dagenham, England.
[6] Eastman Kodak Co., Rochester, N. Y.
[7] E. Merck, Darmstadt, Germany.
[8] Farbwerke Hoechst A.G., Frankfurt, Germany.
[9] Ferranti Ltd., Moston, Manchester 10, England.