

The quaternary salts (QS1 to 11) used in the condensations are numbered as follows.

QS1 2-Iodoquinoline ethiodide	QS6 Quinaldine ethiodide
QS2 2-Iodopyridine methiodide	QS7 Lepidine ethiodide
QS3 2-Iodopyridine ethiodide	QS8 α -Picoline methiodide
QS4 1-Methylbenzoxazole ethiodide	QS9 α -Picoline ethiodide
QS5 1-Methylbenzoselenazole ethiodide	QS10 γ -Picoline metho- <i>p</i> -toluenesulfonate
	QS11 γ -Picoline etho- <i>p</i> -toluenesulfonate

QS10 was prepared by heating equimolecular proportions of γ -picoline and methyl-*p*-toluenesulfonate at 100° for fifteen minutes. QS11 was similarly prepared from ethyl-*p*-toluenesulfonate, heating at 100° for ninety minutes. Both salts were used without purification.

Summary

1. Triethylamine is superior to potassium hydroxide as a condensing agent for the prepara-

tion of 2'-cyanines. Thus, 1',2-diethyloxa-2'-cyanine iodide is obtainable in a yield of 43% using triethylamine, whereas with potassium hydroxide the yield is only 3%. A seleno-2'-cyanine has also been prepared.

2. The use of triethylamine also greatly facilitates the preparation of 1,1'-diethyl-2-pyrido-2'-cyanine iodide; a 2-pyrido-4'-cyanine and a 4-pyrido-2'-cyanine have likewise been prepared by its aid.

3. The failure of potassium hydroxide in the preparation of dyes of the 2,2'-pyridocyanine series has been recorded previously, but using triethylamine these dyes are readily available. Two 2,4'-pyridocyanines have also been prepared.

4. The absorption characteristics of the new dyes are given.

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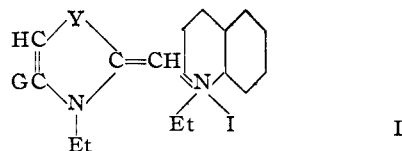
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Studies in the Cyanine Dye Series. IV

By L. G. S. BROOKER, G. H. KEYES AND F. L. WHITE

Up to the present no 2'-cyanine has been described in which the nucleus linked to quinoline consists of a simple 5-membered ring. In a number of instances it has been found that cyanine dyes containing single ring nuclei are difficult to prepare. For example, the thiazolocarbo-cyanines derived from 2,4-dimethylthiazole were obtained in very much smaller yields than the thiocarbo-cyanines derived from 1-methylbenzothiazole, and furthermore, whereas the latter base readily gave rise to thiacyanines, the simple thiazolocyanines could not be prepared by the same method.¹

We have now found, however, that when an equimolecular mixture of 2-methylthiazole ethiodide and 2-iodoquinoline ethiodide is treated with triethylamine, the simplest member of a new group of cyanine dyes, the thiazolo-2'-cyanines, is produced.² This dye, 1',3-diethylthiazolo-2'-cyanine iodide (I, Y = S, G = H) is formed in



(1) Fisher and Hamer, *J. Chem. Soc.*, 2502 (1930).
 (2) Brooker, U. S. Patent 1,989,446.

excellent yield, and 2,4-dimethylthiazole ethiodide and 2-methyl-4-phenylthiazole ethiodide likewise give good yields of the corresponding dyes.

These new thiazolo-2'-cyanines give yellowish-orange solutions. The absorption maximum of the 1',3-diethyl compound is at 4650 Å., and there is a secondary band nearer the red (Fig. 2, B). Introduction of a 4-methyl group shifts the maximum to 4725 Å. (Fig. 1, B) and there is still a secondary band nearer to the red, but in this case it is less pronounced. Replacement of 4-methyl by 4-phenyl produces no further shift, a fact which is worthy of notice, considering that the methyl and phenyl groups have very different effects as δ -substituents in dyes of the thia- and selenocarbo-cyanine series.³

Dyes of the 2'-cyanine series containing the benzoxazole and benzoselenazole nuclei have been described⁴ and we have now prepared certain related dyes containing the simple oxazole and selenazole nuclei. 2-Methyloxazole has not itself been prepared, but certain of its substituted derivatives have been known for a long time. Of

(3) Brooker and White, *THIS JOURNAL*, 57, 2480 (1935).
 (4) Brooker and Keyes, *ibid.*, 57, 2488 (1935).

these, 2,4-dimethyloxazole was prepared by Schuftan⁵ and 2-methyl-4-phenyloxazole by Blümlein.⁶ Quaternary salts of these bases also react with 2-iodoquinoline alkyl iodides, giving oxazolo-2'-cyanines.² Thus, 2,4-dimethyloxazole etho-*p*-toluenesulfonate gives 1',3-diethyl-4-methyloxazolo-2'-cyanine iodide (I, Y = O, G = Me) while 2-methyl-4-phenyloxazole etho-*p*-toluenesulfonate similarly yields 1',3-diethyl-4-phenyloxazolo-2'-cyanine iodide (I, Y = O, G = Ph). These dyes give yellow solutions and their absorption curves are almost identical; the maxima are at 4350 Å. and in each case there is evidence of a secondary band nearer the red (Fig. 1, A).

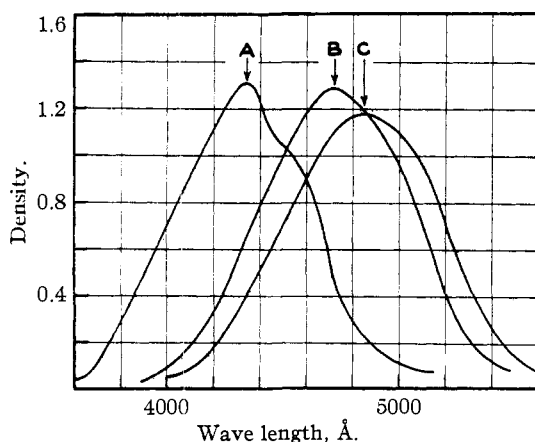


Fig. 1.—Absorption curves of 1:60,000 solutions of 2'-cyanines: A, 1',3-diethyl-4-methyloxazolo-2'-cyanine iodide; B, 1',3-diethyl-4-methylthiazolo-2'-cyanine iodide; C, 1',3-diethyl-4-methylselenazolo-2'-cyanine iodide.

Bases of the 2-methylselenazole series have not hitherto been described but we have prepared 2,4-dimethylselenazole⁷ by the action of chloroacetone on selenoacetamide.⁸ The new base has an odor very like that of 2,4-dimethylthiazole and its ethiodide underwent condensation with 2-iodoquinoline ethiodide to give 1',3-diethyl-4-methylselenazolo-2'-cyanine iodide² (I, Y = Se, G = Me). The absorption curve of this dye shows a principal maximum at 4850 Å. and has a secondary band nearer the red (Fig. 1, C). The effect of replacing the sulfur atom in 1',3-diethyl-4-methylthiazolo-2'-cyanine iodide by selenium is therefore to shift the absorption maximum 125 Å. toward the red, this being a greater difference than

(5) Schuftan, *Ber.*, **28**, 3070 (1895); see also Oesterreich, *ibid.* **30**, 2254 (1897).

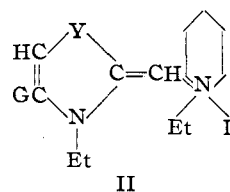
(6) Blümlein, *ibid.*, **17**, 2578 (1884); see also Lewy, *ibid.*, **20**, 2576 (1887); **21**, 924 (1888).

(7) Brooker and White, U. S. Patent 2,005,411.

(8) Kindler, *Ann.*, **431**, 187 (1923).

that between the absorption maxima of the related thia- and seleno-2'-cyanines.⁴ The difference between the positions of maximum absorption of the oxygen and sulfur containing dyes of the series shown in Fig. 1 is again considerably greater than that between the sulfur and selenium containing dyes.

Triethylamine has also been applied to the condensation of quaternary salts of the 2-methylthiazoles with 2-iodopyridine alkyl iodides. Thus, from 2-methylthiazole ethiodide there was obtained 1',3-diethylthiazolo-2'-pyridocyanine iodide (II, Y = S, G = H), the absorption maximum of which is at 4425 Å. (Fig. 2, A). The



related 4-methyl and 4-phenyl dyes were similarly prepared, and these two dyes have similar absorption curves but with maxima at 4475 Å. From 2,4-dimethylselenazole ethiodide there was similarly prepared 1',3-diethyl-4-methylselenazolo-2'-pyridocyanine iodide (II, Y = Se, G = Me), the absorption maximum of which is at 4550 Å.

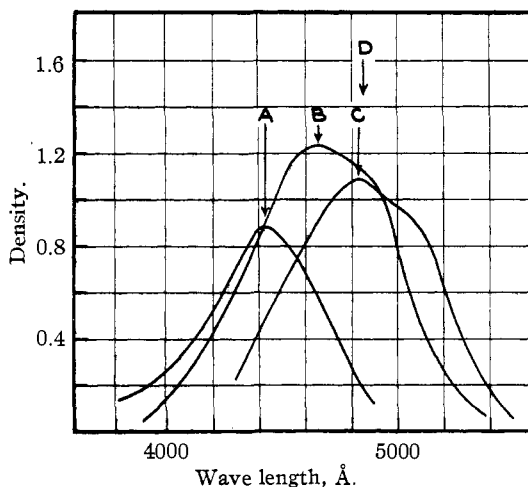
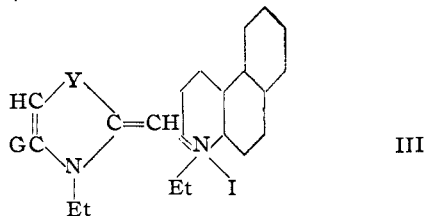


Fig. 2.—Absorption curves of dyes derived from 2-methylthiazole ethiodide: A, 1',3-diethylthiazolo-2'-pyridocyanine iodide (1:75,000); B, 1',3-diethylthiazolo-2'-cyanine iodide (1:60,000); C, 1',3-diethyl-5',6'-benzo-thiazolo-2'-cyanine iodide (1:75,000).

Triethylamine also proved satisfactory for the condensation of quaternary salts of the 2-methylthiazoles with 2-iodo- β -naphthoquinoline alkyl

iodides. Thus, 2-methylthiazole ethiodide yielded 1',3-diethyl-5',6'-benzo-thiazolo-2'-cyanine iodide (III, Y = S, G = H); maximum absorption 4830 Å. (Fig. 2, C).



It will be seen from Fig. 2 that if a benzene residue is attached to 1',3-diethylthiazolo-2'-pyridocyanine iodide (A) so as to give the thiazolo-2'-cyanine (B) the absorption maximum undergoes a shift toward the red of 225 Å. If a benzene residue is attached in turn to 1',3-diethylthiazolo-2'-cyanine iodide (B) so as to give the 5',6'-benzo-thiazolo-2'-cyanine iodide (C) the absorption maximum is shifted 180 Å. nearer the red. It is interesting to note that this is very near the position of maximum absorption of the isomeric 1',2-diethylthia-2'-cyanine iodide (Fig. 2, arrow D) (Fig. 1, B in Part III of this series⁴).

From the appropriate quaternary salts there were also obtained 1',3-diethyl-4-methyl- and 1',3-diethyl-4-phenyl-5',6'-benzo-thiazolo-2'-cyanine iodides and both of these have absorption maxima at 4875 Å. All three of the 5',6'-benzo-thiazolo-2'-cyanines have secondary bands nearer the red.

By a similar reaction 2-methyl-4-phenyloxazole gave rise to 1',3-diethyl-4-phenyl-5',6'-benzoxazolo-2'-cyanine iodide (III, Y = O, G = Ph), which has its maximum absorption at 4475 Å. and 1',3-diethyl-4-methyl-5',6'-benzoselezazolo-2'-cyanine iodide (III, Y = Se, G = Me) was prepared from 2,4-dimethylselenazole ethiodide. The broad absorption band of this dye has its maximum at 5000 Å. Both of these last named dyes have secondary absorption bands nearer the red.

The new dyes act as photographic sensitizers for the blue and green portions of the spectrum and details are given in the Experimental Section.

The absorption curves were determined for methyl alcoholic solutions, the methods used being those already detailed.⁹ We wish to acknowledge our indebtedness to Mr. E. E. Richardson and Dr. L. A. Jones, who furnished the curves shown in this paper and in Parts II and III. We are also very grateful to Dr. L. T. Hallett, who carried out

(9) Brooker and White, *THIS JOURNAL*, **57**, 547 (1935).

the analyses for all three papers, and to several other colleagues for sensitizing data.

Experimental

Selenoacetamide was prepared by a modification of Kindler's method,⁸ and we are much indebted to Dr. R. H. Bullard for advice and help with this preparation. The hydrogen selenide, generated by heating a mixture of ferrous selenide and 12 *N* sulfuric acid, was first passed through a series of traps standing in a freezing mixture to remove excess moisture and then through a calcium chloride tower. About 90 g. of the gas (roughly three-quarters of the calculated amount) was dissolved in the chilled (-10°) mixture of acetonitrile (61.5 g.) and absolute ethyl alcohol (1 liter) in which sodium (4.5 g.) had previously been dissolved, all air having already been swept out of the apparatus with a current of nitrogen. After allowing to stand in the freezing mixture overnight, the flask was connected to a mercury manometer and gradually heated to 60°, being maintained at this temperature until the absorption of hydrogen selenide was practically complete. At no time did the excess pressure exceed 720 mm. of mercury. This process required, on an average, a total of about nine hours' heating. The reaction mixture was filtered after allowing it to cool slowly overnight, the filtrate evaporated to dryness under reduced pressure and the residue extracted with boiling benzene. The selenoacetamide crystallized out on chilling the solution and was removed and freed from adhering solvent by standing in a vacuum desiccator. The average yield of several experiments, based on the amount of hydrogen selenide added, was 60%, the highest being 77%. The unstable selenoacetamide was used as soon as possible.

2,4-Dimethylselenazole.—A mixture of chloroacetone (22.7 g., 1 mol) and absolute ethyl alcohol (10 cc.) was warmed on the steam-bath and selenoacetamide (30 g., 1 mol) added in small portions with shaking. A vigorous reaction occurred after each addition. After a further ten minutes' heating, the mixture was allowed to cool and water (100 cc.) was added followed by excess of 45% sodium hydroxide solution. The base was extracted with ether, the ethereal layer dried over anhydrous potassium carbonate, filtered, and the solvent removed by evaporation. The base was purified by fractionation; yield 41%, b. p. 55–58° (13 mm.). After a further fractionation the main portion of the base passed over at 54–55° (12 mm.).

Anal. Calcd. for C₆H₇NSe: C, 37.45; H, 4.40. Found: C, 38.10; H, 4.48.

Quaternary Salts.—The quaternary salts used in the condensations are numbered as follows

QS1 2-Iodoquinoline ethiodide	QS6 2-Methyl-4-phenylthiazole ethiodide
QS2 2-Iodopyridine ethiodide	
QS3 2-Iodo-β-naphthoquinoline ethiodide	QS7 2,4-Dimethylselenazole etho- <i>p</i> -toluenesulfonate
QS4 2-Methylthiazole ethiodide	QS8 2-Methyl-4-phenyloxazole etho- <i>p</i> -toluenesulfonate
QS5 2,4-Dimethylthiazole ethiodide ¹	QS9 2,4-Dimethylselenazole ethiodide

In the preparation of QS7, equimolecular proportions of the base and ethyl *p*-toluenesulfonate were heated at 100° for one day. QS8 was similarly prepared, but the components were heated for two days. In both cases

viscous melts were formed and were used without purification. Three new ethiodides are listed in Table I. These were obtained by the usual method of heating the base on the steam-bath under reflux with excess of ethyl iodide (10% excess for QS4, 100% excess for QS6 and QS9)

with exclusion of light and moisture. The products were ground with and well washed with solvent (ether for QS4, acetone for QS6 and QS9) and the nearly colorless powders were sufficiently pure for further use. The yields given correspond to this stage.

TABLE I
PREPARATION OF QUATERNARY SALTS

Quaternary salts	Heating, days	Yield, %	M. p., °C.	Formula	Calcd.	Analyses, % Found
QS4	1	83	195-197 ^a	C ₈ H ₁₀ INS	I, 49.77	49.79 ^a
QS6	6	44	175.5-176.5 ^b	C ₁₂ H ₁₄ INS	I, 38.33	38.34 ^b
QS9	2	87	157-158 ^c	C ₇ H ₁₂ INSe	I, 40.14	40.53 ^c

^a After a second treatment with ether. ^b After recrystallization from acetone; colorless crystals. ^c After recrystallization from very little methyl alcohol; colorless crystals.

TABLE II
PREPARATION OF DYES

2'-Cyanine iodides	Quaternary Salt	G.	NEts, g.	EtOH, cc.	Heated min.	Yield, %	Solvent, cc./g.	M. p., °C. dec.	Formula	Analyses, % Calcd.	% Found
D1 1',3-DiEt-thiazolo-	QS4	2.5	2.1	20	20	80; 61	MeOH	267-	C ₁₇ H ₁₉ IN ₂ S	I, 30.94	31.20
	QS1	4.1					15	269			
D2 1',3-DiEt-4-Me-thiazolo-	QS5	2.7	2.1	23	20	80; 66	MeOH	255-	C ₁₈ H ₂₁ IN ₂ S	I, 29.92	29.91
	QS1	4.1					15	257			
D3 1',3-DiEt-4-Ph-thiazolo-	QS6	3.3	2.1	23	20	86; 76	MeOH	256-	C ₂₃ H ₂₃ IN ₂ S	I, 26.10	26.18
	QS1	4.1					50	258			
D4 1',3-DiEt-4-Me-oxazolo- ^a	QS7	6.0	4.2	25	10	53; 49	MeOH	255-	C ₁₈ H ₂₁ IN ₂ O	I, 31.10	30.90
	QS1	8.2					20	258			
D5 1',3-DiEt-4-Ph-oxazolo- ^a	QS8	13.5	8.0	25	20	25; 19	MeOH	262-	C ₂₃ H ₂₃ IN ₂ O	I, 27.00	26.89
	QS1	15.5					75	264			
D6 1',3-DiEt-4-Me-selenazolo-	QS9	3.16	2.1	20	15	73; 62	MeOH	259-	C ₁₈ H ₂₁ IN ₂ Se	I, 26.93	26.97
	QS1	4.1					17	260			
2'-Pyridocyanine iodides											
D7 1',3-DiEt-thiazolo-	QS4	2.5	2.1	10	20	44; 31 ^b	MeOH	260-	C ₁₃ H ₁₇ IN ₂ S	I, 35.25	35.37
	QS2	3.6					15	262			
D8 1',3-DiEt-4-Me-thiazolo-	QS5	2.7	2.1	13	20	53; 35	MeOH	255-	C ₁₄ H ₁₉ IN ₂ S	I, 33.92	34.12
	QS2	3.6					10	257			
D9 1',3-DiEt-4-Ph-thiazolo-	QS6	3.3	2.1	18	20	57; 30 ^b	MeOH	247-	C ₁₉ H ₂₁ IN ₂ S	I, 29.10	29.18
	QS2	3.6					30	249			
D10 1',3-DiEt-4-Me-selenazolo-	QS9	1.58	1.1	^c	20	33; ^d 24	H ₂ O ^e	232-	C ₁₄ H ₁₉ IN ₂ Se	I, 30.12	30.28
	QS2	1.8					50	233			
2'-Cyanine iodides											
D11 1',3-DiEt-5',6'-benzo-thiazolo-	QS4	1.3	1.1	15	20	56; ^f 24	EtOH	268-	C ₂₁ H ₂₁ IN ₂ S	I, 27.58	27.58
	QS3	2.3					340	270			
D12 1',3-DiEt-4-Me-5',6'-benzo-thiazolo-	QS5	0.7	0.6	18	20	50; 33	MeOH	278-	C ₂₂ H ₂₃ IN ₂ S	I, 26.76	26.85
	QS3	1.1					165	280			
D13 1',3-DiEt-4-Ph-5',6'-benzo-thiazolo-	QS6	0.8	0.6	13	20	54; 42	MeOH	274-	C ₂₇ H ₂₅ IN ₂ S	I, 23.67	23.67
	QS3	1.1					100	276			
D14 1',3-DiEt-4-Ph-5',6'-benzo-oxazolo-	QS8	3.6	2.1	10	40	2.5; ^g	MeOH	279-	C ₂₇ H ₂₅ IN ₂ O	I, 24.40	24.26
	QS3	4.6				1.5	115	282			
D15 1',3-DiEt-4-Me-5',6'-benzo-selenazolo-	QS9	1.05	0.75	20	20	60; 49	MeOH	275-	C ₂₂ H ₂₃ IN ₂ Se	I, 24.36	24.46
	QS3	1.53					105	277			

^a A small amount of unused QS1 was removed from the hot reaction mixture by filtration and the filtrate deposited the dye on cooling. ^b After two recrystallizations. ^c 10 cc. of *n*-PrOH used as solvent, reaction mixture being heated at 100°. ^d The dye was precipitated from the reaction mixture with ether and impurities removed with acetone. ^e The solution of the dye in hot water was twice refluxed for five minutes with norite, taking of this, on each occasion, one-twentieth of the weight of the dye. ^f The crude dye required treating with hot water and a little piperidine to remove unchanged QS3; it was then recrystallized three times from EtOH. ^g The dye was precipitated by adding ether (100 cc.) with chilling and was washed with water.

Dyes.—The dye condensations are listed in Table II. They were carried out as already detailed.⁴ The yields of crude and of purified dyes are given and the volume of solvent required for recrystallization.

D1 formed red needles with a blue reflex, 2 and 3 being similar; 4 and 5 consisted of yellow-brown prisms, 6 reddish-brown needles, 7 yellow-orange tablets, 8 brownish-yellow crystals, 9 light-brown prisms; 10 consisted of amber needles; 11 formed minute orange-brown crystals with a green reflex, and 12, 13 and 15 all consisted of reddish-brown needles with a green reflex; 14 formed reddish-brown crystals.

The dyes were tested photographically by incorporation in a chloride emulsion. The maximum effect of D1 is at about 5175 Å., the effect extending to about 5500 Å. for the moderate exposure given. D2 and 3 both have maxima at 5250 Å., and D6 at 5350 Å. D4 and 5 both have maxima at 4775 Å. The order in which these dyes fall is the same, therefore, whether absorption or sensitizing maxima are considered with respect to increasing wave length, and the difference between corresponding absorption and sensitizing maxima varies from 425 to 525 Å.

In the 2'-pyridocyanine series the sensitizing maxima of D7 to 10 lie at 4700, 4750, 4750, and 4825 Å., respectively, and in the series D11 to 15 the corresponding figures are 5250, 5300, 5300, 4900 and 5400 Å., respectively.

Summary

1. Triethylamine has proved to be an excellent condensing agent for the preparation of the hither-

to unknown thiazolo-2'-cyanines from quaternary salts of the 2-methylthiazoles and 2-iodoquinoline ethiodide. Three dyes of this series are described.

2. By using 2-iodopyridine ethiodide and 2-iodo- β -naphthoquinoline ethiodide there have likewise been prepared the corresponding thiazolo-2'-pyridocyanines and 5',6'-benzo-thiazolo-2'-cyanines, respectively.

3. Bases of the 2-methyloxazole series have been used for the preparation of certain oxygen-containing dyes related to the above, and 2,4-dimethylselenazole has been synthesized and similarly applied to the formation of corresponding cyanine dyes.

4. Four dyes have been prepared in which there is a methyl substituent in the 4-position of the thiazole (or oxazole) nucleus. In every case the absorption maximum occurs at the same wave length as that of the related dye containing a 4-phenyl group. Further absorption relationships are discussed.

5. The new dyes are all photographic sensitizers and details of their action are given.

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

A Study of Some Urea Derivatives in the Terpene Series

BY ROBERT L. BATEMAN AND ALLAN R. DAY

In connection with certain studies of urea and its derivatives, it was thought that the preparation and examination of some terpenyl ureas might be of interest. While certain of the terpenes and their derivatives are employed medicinally, little experimental work has been carried out with the purpose of modifying their properties by structural changes and little effort has been made to introduce terpene radicals into compounds of known physiological properties.

Menthyl and bornyl ureas and certain of their derivatives were chosen because of the known physiological properties of substituted ureas and because of the medicinal importance of menthol and camphor which were the starting materials. Menthol is known to possess mild antiseptic and anesthetic properties, while camphor acts as a depressant on the central nervous system and as a

stimulant on the circulatory system. If these properties, in greater part, are inherent in the functional groups (hydroxyl and carbonyl, respectively) the introduction of the menthyl and bornyl radicals into urea would not be expected to produce marked effects, as the functional groups are absent. However, if their physiological properties depend in part on their cyclic structure, a definite modifying influence should be observed.

It will be noted that all but one of the derivatives prepared contain the simple menthyl or bornyl group. In order to determine the influence of the functional group, 2-keto-3-carbamido-camphane was prepared. This urea contains in its substituent not only the cyclic structure common to borneol and camphor, but also the functional group of camphor.

The terpenylureas were obtained in satisfactory