Torino, Istituto Chimico della Università
Roma, Università Cattolica del S. Cuore, Facoltà di Medicina,
Istituto di Chimica, Centro Nazionale Chimica del Farmaco, Sezione II^

The Synthesis and Structure of Methyl- and Dimethylthiazoloquinolines

Gaetano Di Modica, Ermanno Barni and Franco Delle Monache

The preparations and properties of new methyl- and dimethylthiazoloquinolines are described. The NMR evidence supports the angular structures of these heterocycles.

In previous papers (1,2) the synthesis and properties of 2,9-dimethylthiazolo[4,5-f]quinoline (I) and 2,9-dimethylthiazolo[5,4-f]quinoline (II) have been described.

The present paper deals with synthesis and properties of similar compounds, particularly 9-methylthiazolo[4,5-f]quinoline (III), 9-methylthiazolo[5,4-f]-quinoline (IV), 2,7-dimethylthiazolo[4,5-f]quinoline (V), 2,7-dimethylthiazolo[5,4-f]quinoline (VI), 7-methylthiazolo[4,5-f]quinoline (VII), 7-methylthiazolo[5,4-f]quinoline (VIII).

The above compounds are particularly interesting for the preparation of polymethene dyes due to the presence of reactive methyl groups.

Thiazololepidines and thiazoloquinaldines have been prepared following the general method of Campbell and Schaffner (3) and of Campbell, Helbing and Kerwin (4). We have condensed methyl vinyl ketone and crotonaldehyde with the following amine hydrochlorides: 2-methyl-5-aminobenzothiazole (IX), 5-aminobenzothiazole (X), 2-methyl-6-aminobenzothiazole (XI), 6-aminobenzothiazole (XII), thus obtaining the above compounds.

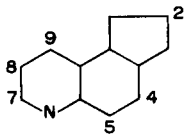
Yields, physical constants, analyses and U. V. data of compounds and of related derivatives are summarized in Table I.

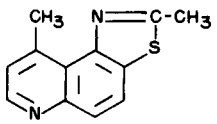
All the described compounds behave as monoacidic bases like some analogous described heterocycles (5,6,7): this is supported by analytical data of ethiodides and picrates. Our U. V. spectral data are substantially in agreement with the statements made by Boggust and Cocker regarding similar substances (8). NMR spectra are reported in figures I-XII (9) and related data are summarized in Table II.

The application of Doebner-Miller reaction to 5- and 6-aminobenzothiazoles could lead to [4,5-f] and [5,4-f] isomers by angular ring closure or to [5,4-g] and [4,5-g] isomers by linear ring closure.

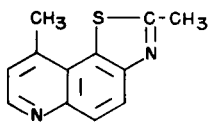
The evidence that angular structure is raised from cyclisation is based on examination of aromatic non pyridine proton signals. In the case of the angular structure the named protons in the *ortho* position would be indicated by an AB quartet with $J_{AB} \cong 7 - 10$ c.p.s., while in a linear structure the J_{AB} constant would be = 1 c.p.s., being the protons in the *para* position. The J value observed for our [5,4-f] isomers is in fact 9 c.p.s., according to the statement for an angular structure. The isomers of [4,5-f] type show a single peak in $CDCl_3$ (Figures I, III, V, VII) due to the fact that in these structures $\delta H_4 = \delta H_5$ (10).

The spectra of [4,5-f] type isomers have been determined in CF_3COOH solution. The action of the acid is the salification of the molecule; the salification affords a different charge distribution which necessarily differentiates the δ values of the aromatic *ortho* protons H_4 and H_5. The spectra (Figures IX-XII) shows in fact in the aromatic non pyridine proton region an AB quartet with J_{AB} = 9 c.p.s. like [5,4-f] isomers in $CDCl_3$.





I



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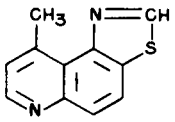

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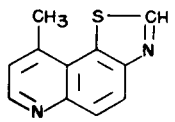
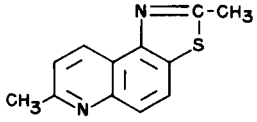


IV



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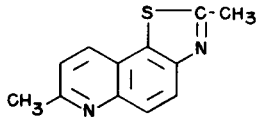

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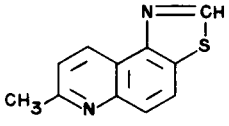

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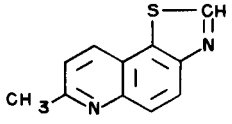


VIII

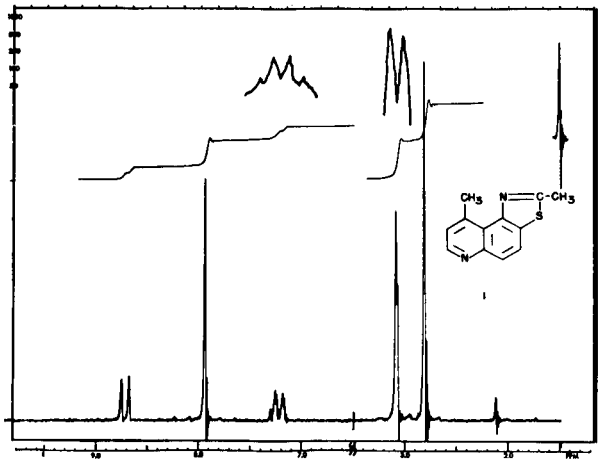


Figure I (a)

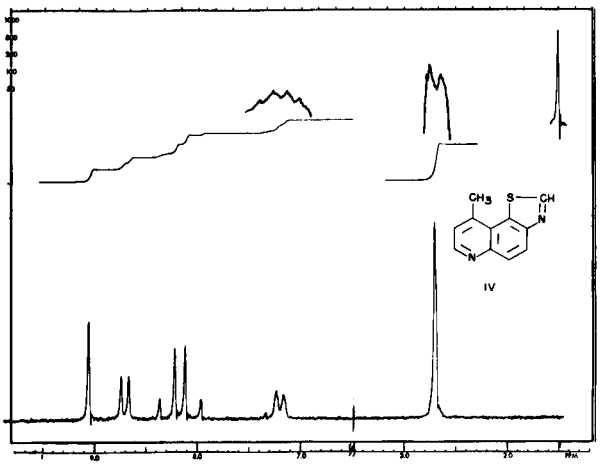


Figure IV (a)

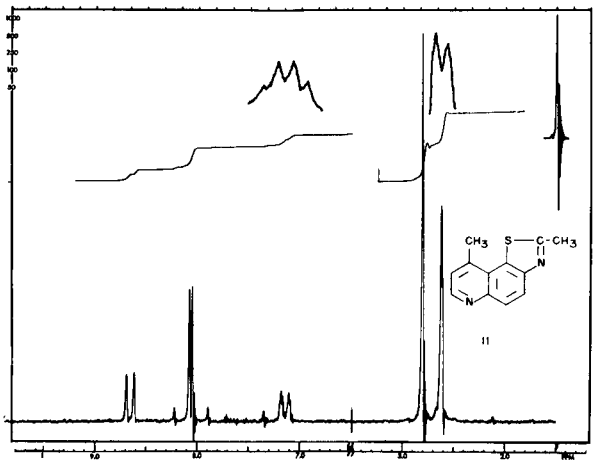


Figure II (a)

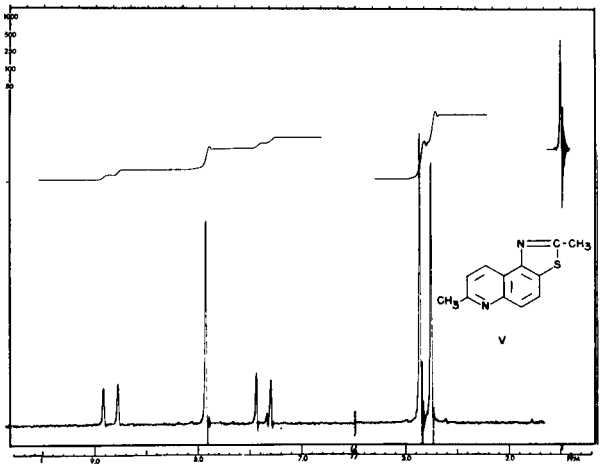
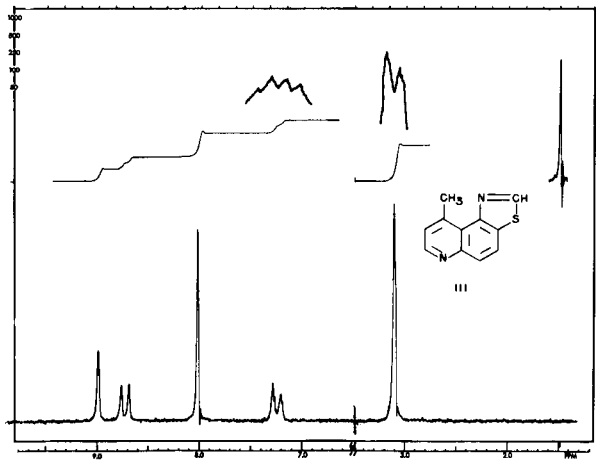


Figure V (a)



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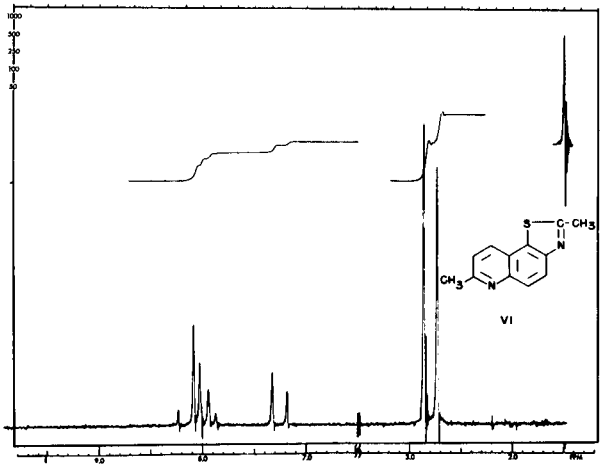

Figure VI (a)

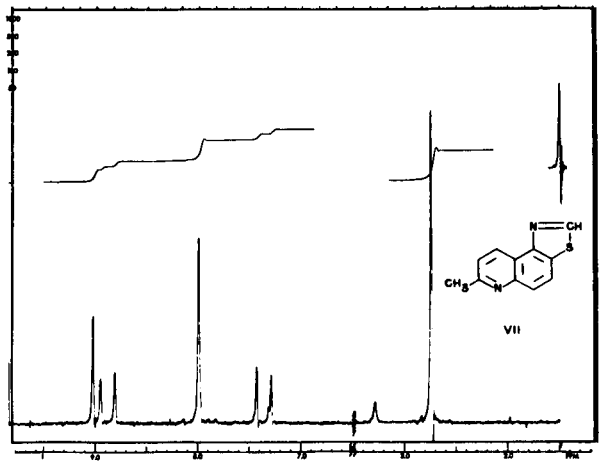

Figure VII (a)

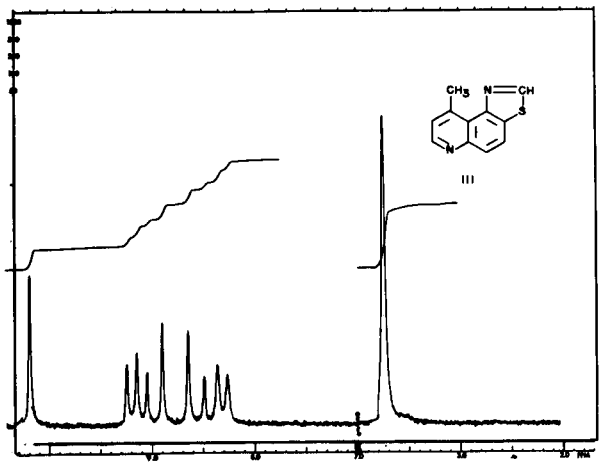

Figure X (b)

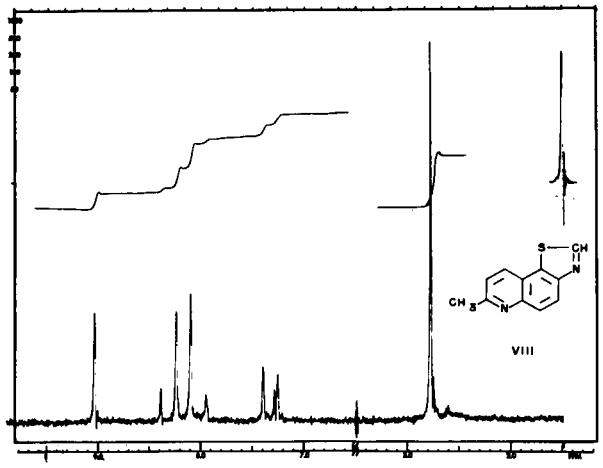

Figure VIII (a)

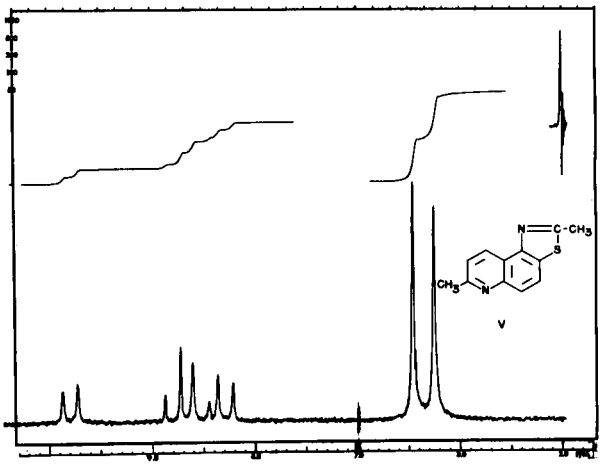

Figure XI (b)

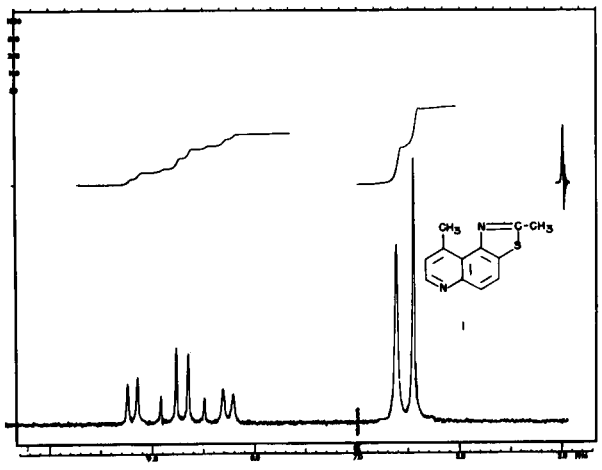

Figure IX (b)

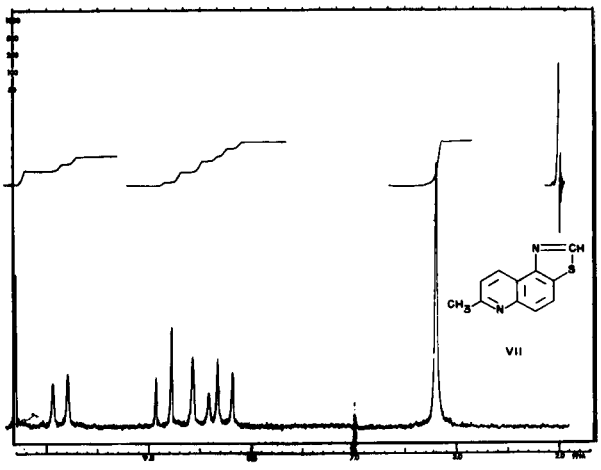

Figure XII (b)

TABLE I

Compound	Yield %	Crystallization	M.P. °C	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Iodine % Calcd.	Iodine % Found	U.V. Spectra λ max (mμ)	U.V. Spectra log ε
I	36	Methanol/water	118-119	67.25	66.86	4.70	4.86	-	-	245	4.74
										300	3.93
										326	3.61
Ethiodide	-	Abs. ethanol/ether	252-253	-	-	-	-	34.27	34.39	-	-
Picrate	-	Ethanol	253	48.76	48.84	2.95	3.06	-	-	-	-
II	32	Methanol/water	149-150	67.25	67.82	4.70	4.91	-	-	252	4.57
										286	3.53
										329	2.78
Ethiodide	-	Abs. ethanol/ether	238-239	-	-	-	-	34.27	34.30	-	-
Picrate	-	Ethanol	279	48.76	48.88	2.95	3.07	-	-	-	-
III	29	Ligroin	108	65.97	66.04	4.02	4.13	-	-	241	4.46
										292	3.63
										326	3.30
Ethiodide	-	Abs. ethanol	220	-	-	-	-	35.63	35.72	-	-
Picrate	-	Benzene	213	47.55	47.68	2.58	2.61	-	-	-	-
IV	31	Ligroin	162	65.97	66.01	4.02	4.11	-	-	248	4.46
										285	3.56
										328	2.56
Ethiodide	-	Abs. ethanol	265	-	-	-	-	35.63	35.78	-	-
Picrate	-	Ethanol	260	47.55	47.68	2.58	2.70	-	-	-	-
V	26	Ligroin	122	67.25	67.66	4.70	4.79	-	-	241	4.46
										300	3.61
										314	3.46
										328	3.33
Ethiodide	-	Abs. ethanol	234	-	-	-	-	34.27	34.32	-	-
Picrate	-	Ethanol/water	245	48.76	48.89	2.95	3.03	-	-	-	-
VI	28	Ligroin	104	67.25	67.38	4.70	4.85	-	-	253	4.54
										319	3.21
										334	3.09
Ethiodide	-	Abs. ethanol	256	-	-	-	-	34.27	34.30	-	-
Picrate	-	Ethanol/water	261	48.76	48.91	2.95	3.00	-	-	-	-
VII	25	Ligroin	116	65.97	66.08	4.02	4.12	-	-	238	4.57
										287	3.69
										311	3.52
										318	3.46
										326	3.56
Ethiodide	-	Abs. ethanol	277	-	-	-	-	35.63	35.74	-	-
Picrate	-	Benzene	260	47.55	47.63	2.58	2.68	-	-	-	-
VIII	16	Light petroleum	128	65.97	66.09	4.02	4.11	-	-	258	4.50
										318	3.29
										333	3.23
Ethiodide	-	Ethanol	201	-	-	-	-	35.63	35.75	-	-
Picrate	-	Ethanol	231	47.55	47.64	2.58	2.69	-	-	-	-

TABLE II

NMR Spectra (a)

Compound	H_2	H_7 (d)	H_8 (d)	H_9 (d)	H_4-H_5	C_2-Me	C_7-Me	C_9-Me	$J_{H_7-H_8}$	$J_{H_8-H_9}$	$J_{H_4-H_5}$	$J_{H_8-C_9-Me}$
I	-	8.73	7.23 (b)	-	7.96	2.82	-	3.09 (d)	4.5	-	-	0.8
II	-	8.68	7.17 (b)	-	8.08 (q)	2.82	-	2.63 (d)	4.5	-	9.0	0.8
III	9.02	8.75	7.27 (b)	-	8.05	-	-	3.13 (d)	4.5	-	-	0.8
IV	9.08	8.72	7.22 (b)	-	8.19 (q)	-	-	2.72 (d)	4.5	-	9.0	0.8
V	-	-	7.38	8.87	7.94	2.88	2.76	-	-	8.5	-	-
VI	-	-	7.27	8.02 (g)	8.06 (f,q)	2.87	2.74	-	-	8.5	9.0	-
VII	9.04	-	7.38	8.89	8.01	-	2.76	-	-	8.5	-	-
VIII	9.04	-	7.34	8.18 (e)	8.19 (c,q)	-	2.78	-	-	8.5	9.0	-

(a) Spectra determined on a Varian A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane (1%) as internal standard. Values given in δ for the first eight columns, in c.p.s. for the others. Singlet are unmarked, multiplet are described as follows: (d) doublet, (q) quartet. All signals in first four columns correspond to one proton, all signals in fifth column to two, all signals in sixth, seventh and eighth, columns to three. (b) Each of the doublet components is split again into a quartet. (c) Superimposed on doublet of H_9. (e) Superimposed on quartet of H_4-H_5. (f) Partially superimposed on doublet of H_9. (g) Partially superimposed on quartet of H_4-H_5.(q) The value indicated is the arithmetic mean between calculated δ_A and δ_B positions of each of the components the AB quartet being δ_A and δ_B (p.p.m.): (II) 8.04, 8.12; (IV) 8.09, 8.29; (VI) 7.98, 8.15; (VIII) 8.07, 8.31.

EXPERIMENTAL

All melting points were taken on a KOFLER melting point apparatus and are uncorrected. Ultraviolet spectra were determined in ethanol on a Beckman DK2 spectrophotometer. Yields, physical constants, analyses and spectral data are summarized in Tables I and II.

2-Methyl-5-aminobenzothiazole (IX).

This compound was prepared by the procedure of Fries and Wolter (6).

5-Aminobenzothiazole (X).

This compound was prepared by the procedure of Spieler and Prijs (11).

2-Methyl-6-aminobenzothiazole (XI).

This compound was prepared by the procedure of Mizuno and Adachi (12).

6-Aminobenzothiazole (XII).

This compound was prepared by the procedure of Boggust and Cocker (8).

Hydrochlorides (IX-XII) were obtained by passing gaseous hydrogen chloride through the ethereal solution of the corresponding amines, and removing the product by filtration.

9-Methylthiazolo[4,5-f]quinoline (III) and 9-Methyl[5,4-f]quinoline (IV).

The general procedure was that of Campbell and Schaffner (3). Modifications have been affected in the isolation of the product from the reaction mixture. In a 500 ml. three necked round bottomed flask, equipped with mechanical stirrer, dropping funnel, reflux condenser, and thermometer were mixed together 11.7 g. (0.063 mole) of (X) or (XII) hydrochloride, 27 g. (0.1 mole) of ferric chloride hexahydrate, 0.1 g. of anhydrous zinc chloride and 45 ml. of 95% ethanol. The flask was heated in an oil bath to an internal temperature of 60° while 3.5 g. (0.05 mole) of methyl vinyl ketone was added dropwise over a period of two hours. The temperature was maintained at 60° for two hours and then the mixture refluxed for two hours and allowed to stand overnight. Most of the ethanol was removed by distillation, the residue made alkaline with 25% sodium hydroxide and subsequently extracted three times with boiling water (steam distillation may be employed but yields are low and this procedure is very slow): hot aqueous extracts were decolorized with carbon black, filtered and cooled. The methylthiazoloquinoline which separated on standing was filtered off; by slowly evaporating the mother liquors additional product was recovered. Total yields of products by this procedure are reported in Table I.

Methyl and Dimethylthiazoloquinolines (V), (VI), (VII), (VIII).

These were prepared by the method of Campbell, Helbing and Kerwin (4). Details of the preparation were the same as for compounds (III) and (IV) using crotonaldehyde instead of methyl vinyl ketone. In the case of compound (VIII) the alkaline mixture obtained after removal of the ethanol was steam distilled and the mother liquor obtained carefully concentrated to one tenth volume. The methylthiazoloquinoline which separated on cooling was removed by filtration.

Ethiodides of compounds (I-VIII) were prepared by mixing together 0.01 mole of base and 0.02 mole of ethyl iodide and heating them in a sealed tube in an oil bath at 100° for eight hours. The ethiodides so obtained were recrystallized as reported in Table I.

Picrates of compounds (I-VIII) were prepared by suspending 0.01 mole of the base in water and dissolving it by addition of a few drops of 20% hydrochloric acid. A slight excess of saturated solution of picric acid in water was then added to the solution. The precipitate was filtered off and recrystallized as reported in Table I.

Acknowledgment.

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REFERENCES

(1) G. Di Modica and E. Barni, *Ann. chim.* (Rome), 54, 530 (1964).

(2) G. Di Modica and E. Barni, *Boll. sci. fac. chim. ind. Bologna*, 22, 56 (1964).

(3) K. N. Campbell and I. J. Schaffner, *J. Am. Chem. Soc.*, 67, 86 (1945).

(4) K. N. Campbell, C. H. Helbing and J. F. Kerwin, *ibid.*, 68, 1842 (1946).

(5) C. Finzi and G. Grandolini, *Gazz. chim. ital.*, 89, 2546 (1959).

(6) K. Fries and A. Wolter, *Ann.*, 527, 60 (1937).

(7) G. E. Calf and E. L. Samuel, *Australian J. Chem.*, 16, 833 (1963).

(8) W. A. Boggust and W. Cocker, *J. Chem. Soc.*, 355 (1949).

(9) Footnotes to Figures I-XII. (a) Spectrum in $CDCl_3$. (b) Spectrum in CF_3COOH.

(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", John Wiley and Sons, Inc., New York-London, 1963, p. 77.

(11) I. Spieler and B. Prijs, *Helv. Chim. Acta*, 33, 1429 (1950).

(12) Y. Mizuno and K. Adachi, *J. Pharm. Soc. Japan*, 72, 745 (1952); *Chem. Abstr.*, 48, 2689 (1954).

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