form solutions of these two dimorphic products were identical.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.79; H, 5.90; N, 3.96 (S).

4-Carbethoxy-4-benzyl-1,5-diphenyl-2,3-pyrrolidinedione (Va).—An ethereal solution of 28.1 g. of crude ethyl ethoxalyldihydrocinnamate[24] and 15.0 g. (0.083 mole) of benzylideneaniline was treated as in the preceding experiments and thus afforded 10.1 g. (29.5%) of Va, m.p. 188.0–188.5°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.53; H, 5.39 (G); N, 3.32 (S).

4-Substituted-1,5-diphenyl-2,3-pyrrolidinediones (4-Substituted-1,5-diphenyl-3-hydroxy-Δ^3-2-pyrrolinones) (III–VI).—Two methods of preparation were used: A. Borsche's procedure[11] in which the appropriate α-ketoacid was warmed with benzylideneaniline in ethanol for a few minutes on the steam-bath. B. Refluxing the corresponding 4-carbethoxy-4-substituted intermediate (IIIa–Va) in methanol containing one equivalent of potassium hydroxide for six hours. Subsequent acidification of the cooled solution afforded the desired product, either as an immediate precipitate or upon evaporation under an air jet.

Acetates were prepared by means of acetic anhydride and sodium acetate,[11] usually being precipitated by dilution with water.

The "anils" (phenylamino derivatives) were prepared by refluxing the compounds with two equivalents of aniline for 2–10 min. After cooling the mixtures were diluted with absolute ethanol, whereupon the derivatives crystallized. Pertinent data are assembled in Table I.

β-Benzylidene-α-ketobutyric Acid.—A procedure described for another substance[25] was adapted for this preparation. By adding 4.6 g. (0.083 mole) of potassium hydroxide in 10 ml. of absolute methanol to 5.6 g. (0.055 mole) of α-ketobutyric acid (*cf.* footnote *b*, Table I for alternative preparations for this substance) and 5.83 g. (0.055 mole) of benzaldehyde dissolved in 10 ml. of absolute methanol, there was obtained 6.9 g. (13%) of the potassium salt of the acid. When a saturated aqueous solution of this salt was acidified with 1.6 *N* hydrochloric acid, an oil separated. It was taken up in ether, dried over magnesium sulfate and recovered as a solid upon filtration and evaporation. Recrystallization from benzene–petroleum ether (90–100°) afforded pure material, m.p. 107.5–108.5°.

(24) W. Wislicenus and M. Munzesheimer, *Ber.*, **31**, 554 (1898).

(25) E. D. Strecher and H. F. Ryder, THIS JOURNAL, **74**, 4392 1952).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.42; H, 5.19 (G).

When run on a larger scale this procedure yielded less tractable material, as did decreasing the relative quantities of methanol. No extensive attempts were made to improve it, however.

Thermal Decomposition of 1,4,5-Triphenyl-2,3-pyrrolidinedione.—This substance was placed in a 50-ml. $ flask connected to a gas buret, as for a Dumas nitrogen determination.[8] The air was displaced by carbon dioxide, and the flask was heated with a flame in such a manner that the gas evolution was moderate and constant. When gas evolution ceased, the apparatus was swept out with carbon dioxide, all gases being collected over 50% potassium hydroxide solution. The residual gas from 1.0 g. of solid was 65.4 ml. (739.4 mm., 25.5°) (85%) and was identified by mass spectrometric analysis as carbon monoxide.[26] The residue in the flask was purified by recrystallization from acetonitrile to give a product, m.p. 333–334°; Borsche[11] had reported 338° (see text). An authentic sample of 2,3-diphenyl-4-hydroxyquinoline[14] melted at the same temperature and showed no depression in melting point upon admixture with the product of this reaction. The infrared spectra were identical.

An acetate was prepared by means of acetic anhydride and sodium acetate. After recrystallization from ethanol–water it melted at 149.5–150.5°.

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.46; H, 4.97 (G); N, 4.13 (S).

Thermal Decomposition of 4-Benzyl-1,5-diphenyl-2,3-pyrrolidinedione.—A 0.5-g. sample was treated as in the preceding experiment. Less extensive decomposition was achieved, but carbon monoxide was again shown to be evolved. The decomposition product was purified by recrystallization from acetone–water, m.p. 262.0–262.5°. The infrared spectrum of this sample is almost identical with that of 2,3-diphenyl-4-hydroxyquinoline.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 85.02; H, 5.86; N, 4.52 (S).

Compounds III and IV did not decompose when subjected to similar treatment.

(26) Very kindly performed by Professor Richard B. Bernstein of this department.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

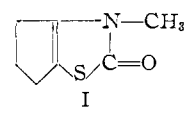
Investigations in Heterocycles. IV.[1] Substituted Cycloalkeno[d]thiazolin-2-ones

BY GEORGE DESTEVENS, ALICE F. HOPKINSON, MARGARET A. CONNELLY, PATRICIA OKE AND DOROTHY C. SCHROEDER

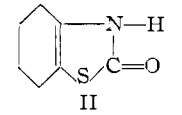
RECEIVED NOVEMBER 19, 1957

The condensation of substituted α-halocycloalkanones with ethyl xanthamidate or ethyl N-methylxanthamidate has resulted in the formation of several new thiazolin-2-ones possessing significant analgetic properties when tested in laboratory animals. These compounds, all cycloalkeno[d]thiazolin-2-ones, are substituted in the 4- or 5-position of the alicyclic ring with a tertiary amino moiety either directly or through a methylene group. The chemistry of the intermediary compounds and the final products is discussed.

In our general program of synthesizing compounds of the thiazolin-2-one class for testing as analgetics, it was found that 2,3,5,6-tetrahydro-3-methyl-4-cyclopentathiazolin-2-one (I) and its six carbon analog, 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one[2,3] (II) raised noticeably the threshold of pain in experimental animals suggesting analgesia.



I



II

Substitutions on the hetero ring nitrogen other than methyl led to a diminution in activity concurrent with an alteration of the toxicity factor. It was thus felt that a more favorable activity–toxicity ratio might be obtained if alterations in structure

(1) For part III of this series: G. deStevens and Angelina Halamandaris, THIS JOURNAL, **79**, 5710 (1957).

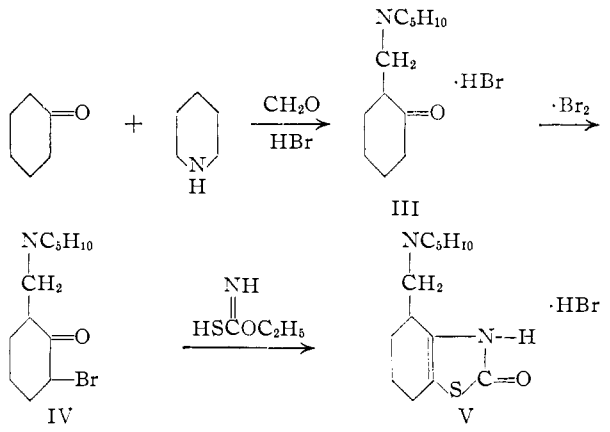
(2) G. deStevens, H. A. Luts and J. A. Schneider, *ibid.*, **79**, 1516 (1957).

(3) G. deStevens, A. Frutchey, A. Halamandaris and H. A. Luts, *ibid.*, **79**, 5263 (1957).

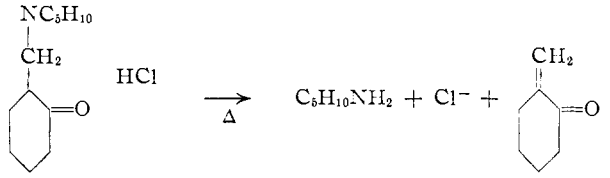
through substitution were made, not on the hetero ring nitrogen, but rather on the alicyclic portion of compounds I and II. A facile approach to this sort of substitution was through the Mannich[4,5] reaction.

The general sequence of reactions leading to the desired product is listed in Scheme I.

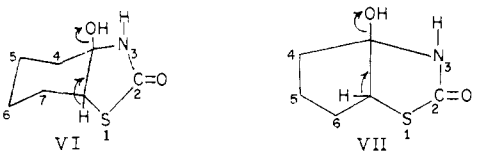
SCHEME I



The over-all yield of V in the above three step synthesis was 40% of theoretical. A large number of variations of the secondary amine in the initial stage of the synthesis was made. However, regardless of the nature of the secondary amine or ketone used, each Mannich condensation was carried out in essentially the same manner. The ratio of alicyclic ketone:secondary amine hydrochloride:38% formaldehyde was 5:1:1, respectively, the excess ketone serving as a diluent. The reaction mixture was heated to the boiling point of the ketone or until reflux occurred. Usually a vigorous reflux period followed which after having spent itself, the reaction mixture was worked up. We have found, as previously reported,[6] that an extensive reflux period only serves to decompose the Mannich base



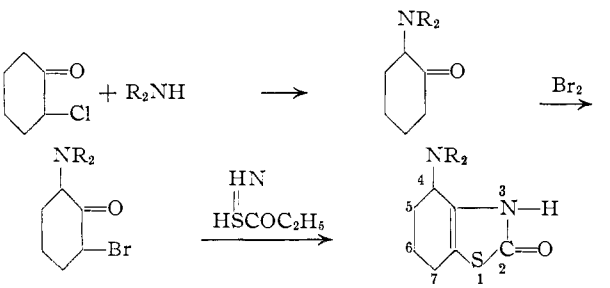
Another interesting feature from a theoretical point of view was the replacement of cyclohexanone in our Mannich condensations with cyclopentanone. The Mannich base, using piperidine, was obtained readily as the hydrobromide.[5] However, it is well-known that α-bromocyclopentanone and its derivatives[7] are extremely unstable, liberating hydrogen bromide readily to yield α,β-unsaturated ketones and further decomposition products. The bromination step thus appeared to be beset with inherent difficulties. An attempt to brominate 2-piperidinomethylcyclopentanone hydrobromide dissolved in glacial acetic acid only led to what appeared to be decomposable polybrominated viscous material. Dissolution of the ketone in glacial acetic containing from 20 to 40% hydrogen bromide, however, shifted the equilibrium in favor of monobromination resulting in 60% yield of desired 2-bromo-5-piperidinomethylcyclopentanone hydrobromide. Much to our surprise this substance was quite stable, no pronounced decomposition occurring when stored at 0° for a period of two weeks. The condensation of the 2-bromoketone with ethyl xanthamidate proceeded at the reflux temperature of ethyl alcohol which served as a solvent. This result was unexpected in the light of our recent work[3] in which α-chlorocyclopentanone condensed with ethyl xanthamidate only under forcing conditions as compared to the mild reaction conditions for the α-chlorocyclohexanone–ethyl xanthamidate condensation. The explanation entertained for the difference in reactivity between these α-halogenated ketones was based on the apparent ease of dehydration of the transition state complex for the six-carbon ring intermediate VI as compared to the corresponding five-carbon ring complex VII. Thus, the *cis* elimination of water in VII appears to involve a higher activation energy than the usually facile *trans* elimination as exemplified by VI. It seems that in the present case, substitution of a piperidino methyl group at position 4 of VII alters, through steric factors, the



conformations of hydroxyl and hydrogen atoms in the molecule in such a way as to facilitate dehydration.

The synthesis of thiazolin-2-one compounds in which the secondary amine was directly attached to carbon 4 of the molecule was carried out in a different manner (see Scheme II).

SCHEME II

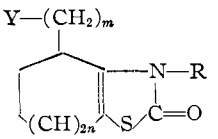


The reaction of the chloroketone with the secondary amine was carried out by a modification of the Mousseron[8] method.

Substitution of the piperidino moiety directly on carbon 5 of a hexahydrobenzothiazolin-2-one required the use of 2-cyclohexenone. This behaves similar to ethyl vinyl ketone in condensation with piperidine. The resulting compound, 3-piperidinocyclohexanone (VIII), upon bromination, can give either the 2- or the 6-bromo derivative. Tenta-

(4) C. Mannich and R. Braun, *Ber.*, 53, 1874 (1920).
(5) C. Mannich and D. Schaller, *Arch. Pharm.*, 276, 575 (1938).
(6) C. Mannich and P. Hönig, *ibid.*, 265, 598 (1927).
(7) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).
(8) M. Mousseron, J. Julien and Y. Jolchine, *Bull. soc. chim. France*, 757 (1952).

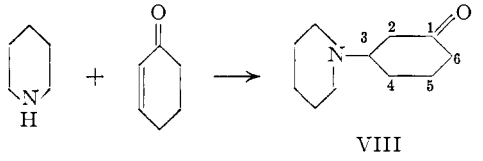
TABLE I



No.	n	m	R	Y	Yield, %[a]	M.p., °C.	Empirical formula[b]	Analyses, % Calcd. C	Found C	Calcd. H	Found H	Calcd. N	Found N	U.v. abs.,[c] λ_{max}, mμ	ε
1	1	0	H	$-N(CH_3)_2$	14.0	206–209	$C_9H_{13}BrN_2OS$	38.86	38.62	5.07	5.51	10.07	9.72	245	5540
2	1	0	CH_3	$-N(CH_3)_2$	5.0	185–187	$C_{10}H_{15}BrN_2OS$	41.10	41.07	5.52	5.82	9.59	9.25	245	5080
3	1	0	H	$-NC_5H_{10}$[d]	10.0	224–226	$C_{12}H_{19}BrN_2OS$	45.14	45.05	6.00	6.01	8.77	8.95	245	5320
4	1	0	CH_3	$-NC_5H_{10}$	5.0	193–195	$C_{13}H_{21}BrN_2OS$	46.84	46.75	6.35	6.41	8.40	8.50	245	4960
5	1	0	H	$-N(C_2H_4)_2O$[e]	12.0	202–204	$C_{11}H_{17}BrN_2O_2S$	41.12	41.44	5.33	5.46	8.72	8.69	245	5200
6	1	0	CH_3	$-N(C_2H_4)_2O$		178–180	$C_{12}H_{19}BrN_2O_3S$	42.99	42.86	5.71	5.80	8.36	8.13	245	4830
7	0	1	H	$-NC_5H_{10}$[d]	11.0	227–229	$C_{12}H_{19}BrN_2OS$	45.28	45.26	6.01	6.30	8.80	8.91	249	4490
8	0	1	CH_3	$-NC_5H_{10}$	42.0	251–252	$C_{13}H_{21}BrN_2OS$	46.85	46.58	6.05	6.31	9.62[h]	9.54[h]	249	4319
9	0	1	H	$-N(C_2H_4)_2O$	13.0	205–208	$C_{11}H_{17}BrN_2O_2S$	41.10	41.07	5.33	5.25				
10	0	1	H	$-NC_6H_{12}$[f]	23.0	189–190	$C_{13}H_{21}BrN_2OS$	46.85	46.58	6.35	6.40	8.40	8.39		
11	1	1	H	$-N(CH_3)_2$	36.0	214–216	$C_{10}H_{17}BrN_2OS$	40.96	41.11	5.84	5.79	9.56	9.30	245	5110
12	1	1	CH_3	$-N(CH_3)_2$	30.0	236–238	$C_{12}H_{19}BrN_2OS$	43.00	43.15	6.23	6.41	9.12	8.91	245	2870
13	1	1	H	$-NC_4H_8$[g]	43.0	238–240	$C_{12}H_{19}BrN_2OS$	45.14	45.03	5.99	6.05	8.77	8.76	246	5110
14	1	1	CH_3	$-NC_4H_8$	30.0	242–244	$C_{13}H_{21}BrN_2OS$	46.84	46.64	6.35	6.39	8.41	8.45	247	4970
15	1	1	H	$-NC_5H_{10}$	60.0	240–242	$C_{13}H_{21}BrN_2OS$	46.84	46.84	6.35	6.44	8.41	8.45	247	4970
16	1	1	CH_3	$-NC_5H_{10}$	30.0	230–232	$C_{14}H_{23}BrN_2OS$	48.41	48.78	6.67	6.98	8.07	7.83	247	4650
17	1	1	H	$-N(C_2H_4)_2O$	38.0	211–213	$C_{12}H_{19}BrN_2O_2S$	42.98	42.97	5.71	5.79	8.36	8.25	246	4930
18	1	1	CH_3	$-N(C_2H_4)_2O$	43.0	230–232	$C_{13}H_{21}BrN_2O_2S$	44.70	44.56	6.06	6.13	8.02	7.73	246	4660
19	1	1	H	$-N(C_5H_9)2CH_3$	34.0	227–229	$C_{14}H_{23}BrN_2OS$	48.42	48.29	6.69	6.62	8.09	7.85	246	4450
20	1	1	H	$-N(C_5H_9)3CH_3$	37.0	242	$C_{14}H_{23}BrN_2OS$	48.42	48.43	6.69	6.59	8.09	8.05	246	5220
21	1	1	H	$-N(C_5H_9)4CH_3$	30.0	248	$C_{14}H_{23}BrN_2OS$	48.42	48.20	6.69	6.69	8.09	8.08	246	5120
22	1	1	CH_3	$-N(C_5H_9)4CH_3$	35.0	255	$C_{15}H_{25}BrN_2OS$	49.86	49.71	6.97	6.94	7.75	7.40	247	4750
23	1	1	H	$-N(C_6H_{12})$	55.0	235–236	$C_{14}H_{23}BrN_2OS$	48.42	48.54	6.72	6.65	8.06	8.31	246	5230
24	1	1	CH_3	$-N(C_6H_{12})$	33.0	220–222	$C_{15}H_{25}BrN_2OS$	49.86	49.80	6.97	7.30			246	4590
25	1	1	H	$-NC_5H_8$-4,4[i]-(C_6H_5)-$(COOC_2H_5)$	15.0	242–244	$C_{22}H_{29}BrN_2O_3S$	54.80	54.45	6.07	6.15			247	5610
26	1	1	CH_3	$-NC_5H_8$-4,4-(C_6H_5)-$(COOC_2H_5)$	25.0	230–232	$C_{23}H_{31}BrN_2O_3S$			6.40[h]	6.00[h]	5.65	5.53	245	4780
27	1	1	H	$-N(C_2H_4)_2NCH_3$[j]	28.0	230–231	$C_{13}H_{23}Br_2N_2OS$			7.47[h]	7.10[h]	9.79	9.62	247	4680
28	1	1	CH_3	$-N(C_2H_4)_2NCH_3$	14.0	226–228	$C_{14}H_{25}Br_2N_2OS$	37.93	37.66	5.84	5.68	9.48	9.10	247	4310
29	1	1	H	$-N(C_2H_4)_2NCH_2CH_2OH$	5.5		$C_{14}H_{25}Br_2N_2O_2S$					9.15	8.95	245	5100
30	1	2	H	$-N(CH_3)_2$	12.0	212–214	$C_{11}H_{19}BrN_2OS$	43.00	43.51	6.23	5.81	9.12	8.95		
31	1	0	H	$-N(C_5H_{10})$		208–210	$C_{12}H_{19}BrN_2OS$	45.14	44.96	6.00	6.28	8.77	8.40	246	5200

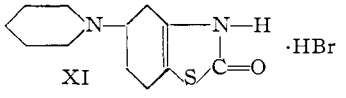
[a] These are calculated on the basis of the α-haloketone–ethyl xanthamidate or ethyl N-methylxanthamidate condensation. [b] The compounds were isolated as mono- or dihydrobromides. [c] All determinations were made on a Beckman recording spectrophotometer, Model DK1; ethyl alcohol was used as the solvent. [d] Piperidine. [e] Morpholine. [f] Hexamethyleneimine. [g] Pyrrolidine. [h] Sulfur. [i] Ethyl-4-phenylisonipecotate. [j] N-Methylpiperazine.

tively, we have assigned the bromo group to carbon 6 on the basis of our experience with this type of reaction in which bromination will always occur on the carbon alpha to the ketone group but furthest removed from the nitrogen.



VIII

Thus, it follows that the final product isolated is assigned formulation IX.



XI

Finally, a series of reactions were carried out (see Scheme III) in order to lengthen by one methylene group the carbon chain at position 4 of the hexahydrobenzothiazoline-2-one.

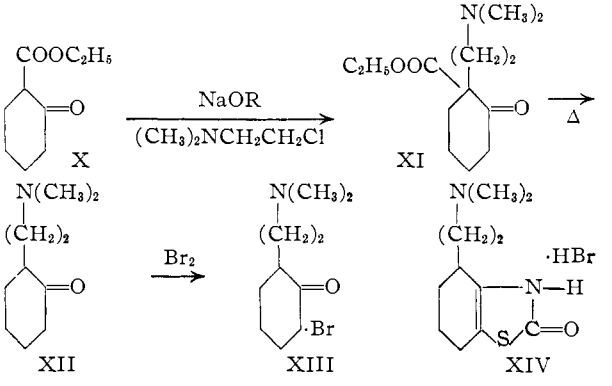
The two steps leading to compound XII have been reported[9] to give yields in the neighborhood of 15% due to the predominant formation of O-alkylated material rather than the desired XI.

(9) W. E. Doering and S. J. Rhoads, THIS JOURNAL, 73, 3082 (1951).

Bromination of XII and condensation of XIII with ethyl xanthamidate proceed normally.

In Table I are presented the analytical data for the compounds prepared.

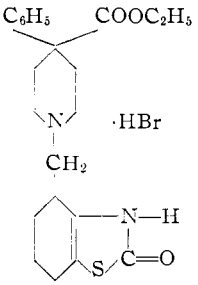
SCHEME III



Pharmacology.—The procedure employed for testing these compounds for analgetic activity is essentially the Wolff–Hardy method as modified by Gross.[2,10] Among the compounds listed in Table I, preparation 15 showed pronounced analgesia in experimental animals. Compound 16, the N-methyl derivative of 15, displayed analgetic

(10) F. Gross, *Helv. Physiol. Acta*, 5, 31 (1947).

properties but with a higher toxicity factor. Compounds 7 and 8, analogs of 2,3,5,6-tetrahydro-4H-cyclopentathiazolin-2-one[2], also displayed analgetic properties. Noticeable decrease in activity was had when the piperidino moiety of compound 15 was exchanged for dimethylamino, pyrrolidino or morpholino, whereas exchange of piperidine for hexamethyleneimine had no adverse effect. It was of interest to determine what analgetic influence the 4-phenyl-4-carbethoxypiperidino moiety[11] would exert when substituted at position 4 of hexahydrobenzothiazoline-2-one. Thus, compounds 25 and 26 were prepared but were found to



be devoid of analgetic properties. These few examples serve to demonstrate the different biological effects associated with apparently slight changes in chemical structure. In a forthcoming report from these Laboratories a more detailed account of the chemical structure–biological function of this class of compounds will be presented.

Acknowledgment.—The authors are grateful to Dr. E. Schlittler for his interest and encouragement throughout this investigation. We would also like to express our gratitude to Dr. J. A. Schneider and his collaborators for the biological testing and to Mr. Louis Dorfman and his associates for the microanalyses and the spectral data.

Experimental[12]

A. General Procedure for Mannich Condensation.—The procedure employed for the Mannich condensations has been described. A mixture of five parts of alicyclic ketone, one part of secondary amine hydrochloride and one part of 38% formaldehyde solution is heated to approximately 100°, whereupon a vigorous reaction occurs. External heat is removed from the flask and the reaction is allowed to proceed of itself. At the end of the reflux period, the solution is chilled immediately to 5°, an equal volume of water is added and the solution is made alkaline to *p*H 9 to 10. This alkaline solution is extracted thoroughly with ether and the ether extract dried over anhydrous K_2CO_3. After drying and filtering, dry hydrogen bromide gas is passed into the filtrate to obtain the hydrobromide salt of the Mannich base. The free bases and their hydrohalide salts have been described in a review.

B. General Procedure for Bromination of Mannich Ketones.—Bromination of the ketones was conducted in 20%–35% hydrogen bromide–acetic acid solution.[13–15]

Essentially the procedure involves dissolving the hydrobromide salt of the Mannich base in 20%–35% hydrogen bromide–acetic acid solution and chilling the solution to 0°. An equivalent amount of bromine is added dropwise. Upon completion of addition, the temperature of the reaction mixture is brought slowly up to room temperature by stirring for approximately one hour. The pale yellow solution is triturated several times with ethyl ether whereupon a crystalline or an oily viscous α-bromoketone was isolated. Some of these bromoketones could be recrystallized only with difficulty and a certain amount of decomposition; the viscous oils resisted all attempts to be recrystallized. Consequently, the bromo derivatives of the Mannich bases were used directly as such for the preparation of the desired thiazolin-2-ones.

C. General Preparation of Thiazolin-2-ones.—The following procedure is typical: Equal molar equivalents of 2-bromo-6-piperidinomethylcyclohexanone and ethyl xanthamidate[16] were added to 200 ml. of ethyl alcohol and the solution was refluxed with stirring for 6 hours.[17] After chilling overnight, the precipitate was collected and recrystallized from 100 ml. of hot water. Other solvents which can be employed for recrystallizing the compounds outlined in Table I are methyl alcohol, ethyl alcohol, *n*-propyl alcohol and isopropyl alcohol.

5-Piperidino-2,3,4,5,6,7-hexahydrobenzothiazolin-2-one (Compound[31] in Table I).—Twenty grams (0.21 mole) of cyclohexenone was added slowly with stirring and external cooling to 19.5 g. (0.21 mole and 10% excess) of piperidine. After standing overnight, the solution was refluxed for one hour. After making the solution strong alkaline, it was extracted with ether and the ether extract dried over Na_2SO_4. The drying salt was filtered off and dry hydrogen bromide gas was bubbled through the filtrate. After several triturations of the viscous residue with dry ether, a tan powder was obtained and recrystallized from a small amount of ethyl alcohol. Crystals of **3-piperidinocyclohexanone hydrobromide**, m.p. 158–160°, were obtained in 45% yield.

Anal. Calcd. for $C_{11}H_{20}BrNO$: C, 50.4; H, 7.67; N, 5.35. Found: C, 49.70; H, 7.82; N, 5.17.

A solution of 8.0 g. (0.036 mole) of 3-piperidinocyclohexanone hydrobromide in 10 ml. of glacial acetic acid containing 20% hydrogen bromide was chilled to 5° and treated dropwise with 5.8 g. (0.026 mole) of bromine dissolved in 5 ml. of glacial acetic acid. Crystals began to form when addition was complete whereupon 20 ml. of ether was added and the mixture stirred for one hour. Chilling, filtering and washing the precipitate with dry ether yielded 8.8 g. of **2-bromo-5-piperidinocyclohexanone hydrobromide**, which was analyzed as such due to its tendency to decompose when attempts were made to recrystallize it.

Anal. Calcd. for $C_{11}H_{19}Br_2NO$: N, 4.11. Found: N, 4.08.

The preparation of the desired **5-piperidino-2,3,4,5,6,7-hexahydrobenzothiazolin-2-one hydrobromide** was carried out as outlined above.

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(11) O. Eisleb, U. S. Patent 2,167,351 (1939).

(12) All melting points in Table I and in this section are uncorrected.

(13) A. H. Land, A. Ziegler and J. M. Sprague, THIS JOURNAL, **69**, 125 (1947).

(14) C. Mannich and T. Goldarch, *Ber.*, **61**, 263 (1928).

(15) C. Djerassi, R. A. Mizzoni and C. R. Scholz, *J. Org. Chem.*, **15**, 700 (1950).

(16) For the preparation of 2,3,4,5,6,7-hexahydro-3-methyl-4-piperidinomethylbenzothiazolin-2-one, the previously described ethyl N-methylxanthamidate (see ref. 3) was used.

(17) From an experimental point of view it is appropriate to note that the extent of reaction was followed by periodically pipetting an aliquot of reaction solution, working it up and submitting the crystalline material to infrared spectroscopic analysis. The presence of 2-bromoketone impurity would exhibit an appreciable band at 1730 cm.$^{-1}$. When the reaction had gone to completion, the 1730 cm.$^{-1}$ was absent and only the 1660 and 1630 cm.$^{-1}$ bands, characteristic for the 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one moiety, were predominant.