Tetracyclic Phenothiazines and Related Compounds. III. Preparation of Cyclic Hydroxypyridones from Arylamines and Malonic Esters[1]

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The position of cyclization in the reaction at elevated temperatures of diethyl ethylmalonate with phenothiazine to give the pyridophenothiazine I has been proved. The influence of some of the factors entering into this condensation (steric hindrance, base strength) has been studied incidental to synthesis of the pyridophenothiazines and pyridophenoxazines (IIIa through IIIf) and the related quinolones in Table I. Clay plate has been found to be an effective catalyst for condensations of alkylmalonic esters with phenothiazine.

Examples of the thermal cyclization of secondary arylamines with monoalkylated malonic esters have been reported infrequently in the literature.[4] Recently this method of making 4-hydroxy-2-quinolones[5] (*cf.* I) has attained some popularity as a method of making intermediates used for the synthesis of alkaloids of the furanocoumarin group.[6] Yields have frequently been poor or unreported.

Our interest in these substances was initiated by our use of this reaction to prepare a tetracyclic phenothiazine derivative I, previously reported[1] in connection with a study of the reductive rearrangement of oximes by lithium aluminum hydride. It seemed likely that this and related compounds might be either carbon-alkylated or oxygen-alkylated by halides corresponding to "pharmacologically active" dialkylaminoalkyl groups, or aminated in the 2- or 3-position by standard reactions, leading to a group of substances of varying sizes, shapes, and polarities, and hence, hopefully, different sorts of potentially useful biological activities. However, difficulties were encountered even in attempts to scale up the preparation of "ethylmalonylphenothiazine" previously reported,[1] and practically no "methylmalonylphenothiazine"[5] was produced under similar reaction conditions even on the same scale. We therefore felt impelled to study certain of the variables which might be changed to improve and allow extension of this reaction of malonic esters and secondary amines. Since the cyclization of diethyl ethylmalonate with phenothiazine would go in poor to fair yield on a small scale, but not on a larger, it was decided to study this reaction in greater detail, and subsequently to see how the facts so obtained needed to be modified when applied to the other systems of interest.

An obvious possible explanation of the poorer yields with increased scale of the reaction was that the reaction might be catalyzed by the (Pyrex) glass surface of the flask used for the reaction, as the flask surface would increase more slowly than the volume with increase in scale of reaction. This might allow intervention to a greater extent of homogeneous side reactions. (Ethanol in theoretical amount is evolved in all cases, whether or not base-soluble product is formed.) Another possibility was that the desired reaction might require nonspecific centers[7] for the evolution of ethanol, which of course would be gaseous at the temperatures (*ca.* 260°) required for reaction. These centers might settle out and so be further from the bulk of the reactants in larger vessels. These possibilities were ruled out by a large number of experiments in which attempted cyclizations were run in the presence of Pyrex glass wool, vermiculite, silica gel, Linde Molecular Sieve No. 4A, neutral or the ordinary chromatographic alumina, powdered boric acid, and others of a variety of available substances. While some of these led to a more rapid evolution of ethanol than occurred in their absence, little or none of the desired product was found on work-up of the reaction products.

Eventually, it was found that unglazed clay plate in the form of a sieved fine powder suspended in the reaction by agitation, or in lumps almost filling the volume occupied by the reactants led to essentially the same yields being obtained with the largest scale used (about one-half kilogram of each reactant) as with the smaller runs. Incidentally, having this information, we tested a group of commercial catalysts suggested[8] as probably being

(1) Previous papers in this series: M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, **80**, 6080 (1958); M. Harfenist, to be published.

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(4) (a) P. Baumgarten and M. Riedel, *Ber.*, **75B**, 984 (1942); (b) R. E. Bowman, A. Campbell, and E. M. Tanner, *J. Chem. Soc.*, 444 (1959); (c) P. Baumgarten and W. Kärgel, *Ber.*, **60**, 832 (1927).

(5) These substances, *e.g.*, I, are properly named as pyridoamines. I, for example, is either 2-ethyl-1,3-diketo-2,3-dihydro-1H-pyrido-[3,2,1-*kl*]phenothiazine or, in its enolic form, 1-keto-2-ethyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine. However, this systematic nomenclature causes the numbering to change with the amine moiety. For example, the carbazole directly analogous to I would be 5-ethyl-4,6-diketo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole. We therefore will use trivial names based on the malonic acid and amine which might be regarded as combining with loss of water to form these compounds. Thus, I will be "ethylmalonylphenothiazine." while its carbazole analog will be "ethylmalonylcarbazole" in direct analogy.

(6) See (a) J. W. Huffman, *J. Org. Chem.*, **26**, 1470 (1960); (b) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **82**, 4395 (1960) for leading references.

(7) M. S. Newman and E. G. Caflisch, Jr., *J. Am. Chem. Soc.*, **80**, 862 (1958).

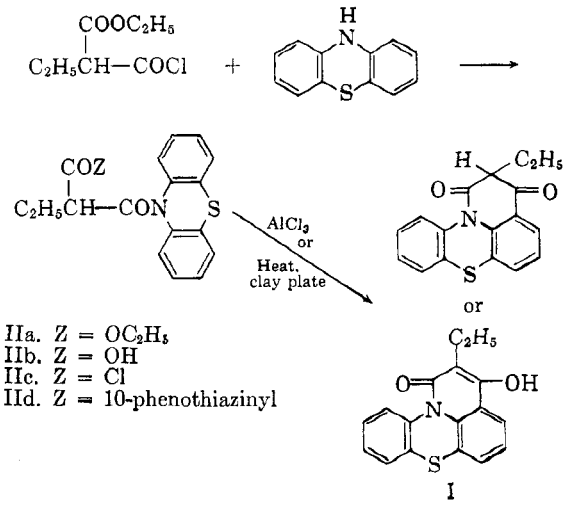
(8) We wish to thank Dr. G. A. Mills, of The Houdry Process Corp., for supplying generous samples of six catalysts.

similar to clay plate in catalytic activity. Two kaolin-based catalysts, surprisingly, gave little of the desired product, and even the best of the catalysts supplied, an alumina-on-silica (S-16, No. 36D2-28Z) was less active than the clay plate, which, with phenothiazine and diethyl ethylmalonate, consistently gave yields averaging about 45–55% of crude acidic material.

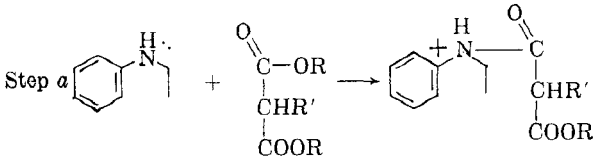
Although the structure of the cyclization products seemed obvious it was thought advisable to prepare our "ethylmalonylphenothiazine" (I)[5] by an alternative, preferably stepwise route. The method selected is outlined below. Ethyl ethylmalonyl chloride was readily prepared from the corresponding mono-ester mono-acid (the monopotassium salt, the immediate product of half-saponification of diethyl ethylmalonate, gave an extremely poor yield, making the small loss on going to the acid very worthwhile), with thionyl chloride. The amide-ester IIa, prepared from this acid chloride and phenothiazine in benzene, was saponified to the amide-acid IIb, which was converted to IIc, again by thionyl chloride. Cyclization of IIc under Friedel-Crafts conditions gave a 73% yield of "ethylmalonylphenothiazine." The points of interest in this almost transparently simple reaction sequence (which, incidentally, could not be made to work at the cyclization step either under Friedel–Crafts conditions or by attempted thermal cyclization, when the starting material was diethyl malonate rather than diethyl ethylmalonate) are the ability to use thionyl chloride, which in other cases has been reported to react with phenothiazine to give presumably ring-chlorinated mixtures, and the intramolecular ring closure into the phenothiazine 1-position, rather than the possible alternative intermolecular acylation into the usually preferred[9] 2-position of a second molecule of phenothiazine.

Having confirmed the structure of these "alkylmalonylheterocycles" both by the alternative synthesis described above, which especially confirms the attachment of the added ring to the phenothiazine nitrogen, and by a conversion of "ethylmalonylcarbazole"[5] to the known 1-acetylcarbazole as part of work reported in another communication, which confirms the other point of attachment of the added ring as *ortho* to the carbazole nitrogen, we are in a position to consider the factors influencing the formation of this ring system in a more precise fashion.

Since the amine reactants in some cases are of types used as free-radical traps (*e.g.* phenothiazine and diphenylamine) we have assumed that the reaction is heterolytic rather than homolytic in type. The reaction presumably starts with the displacement of an alkoxy group from the malonic ester by the formally uncharged nitrogen of the arylamine ("step *a*"). That it is the nitrogen



rather than the *ortho* position in the aromatic ring which is the initiating nucleophile is to be anticipated on grounds of general chemical experience, and this is supported by the isolation from reactions which do not give cyclized product[4c,10]



of malondiamides. That the uncharged nitrogen is the nucleophile, rather than anionic nitrogen produced by loss of proton to trace amounts of base, is suggested by the relative ease of reaction and high yield obtained from reaction of the various alkylanilines with diethyl ethylmalonate which are shown in Table I, lines 1–4, as compared with the higher temperature required to give even a poorer yield of product in the reaction of the same ester with the far more acidic[11] diarylamines, phenothiazine and carbazole (Table I, lines 7 and 8).

It was next necessary to determine the relative rates of step *a*, the initial nucleophilic attack by nitrogen, and of step *b*, the cyclization presumably

(9) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(10) For example, reaction of bis(2,4-dichlorophenyl) benzylmalonate with indole: see Ziegler, *et al.*[13] Also reaction of diethyl ethylmalonate with *o*-anisidine.[6b] Our results with diethyl ethylmalonate and indole are not so clear-cut, but one of the products which we obtained appears to be the result of N-acylation. Since we have found (Table, I line 1 *vs.* line 2) that the homogeneous reaction (i.e. without clay plate) of methylaniline with diethyl ethylmalonate occurs at essentially the same rate as this reaction in the presence of clay plate, we hope to investigate this point further by determining the rate of reaction of appropriately substituted N-alkylanilines.

(11) The greater acidity of diarylamines such as phenothiazine and carbazole compared with that of alkylanilines is an assumption, of course, but a highly probable one, based on the known far lower basicity of phenothiazine compared to the alkylanilines, i.e., it seems reasonable to assume that loss of a proton from an amine R_2NH as compared to loss of a proton from $R_2'NH$ will occur in the same relationship as loss of protons from the conjugate acids $R_2NH_2^+$ and $R'_2NH_2^+$.

TABLE I

RELATIVE RATES AND YIELDS IN REACTIONS OF PHENYLAMINES WITH DIETHYL ETHYLMALONATE

Amine taken	Procedure[a]	Scale[b]	Bath temp., °C.	Half time/ total time	Yield,[c] %
$C_6H_5NHCH_3$	A (300 g.)	500	230 ± 15; 255 ± 8	2.3/6.3	93.1
	B	500	230 ± 15; 255 ± 8[d]	2.3/6.3	91.4[d]
$C_6H_5NHC_3H_7(n)$[e]	A (300 g.)	490	250; 270	2.5/10.3	90
$C_6H_5NHC_3H_7$(iso)[f]	A (450 g.)	330	255; 262	1.3/5	84
Indoline[g]	A (300 g.)	500	230; 245	1/4.5	86
2-Methylindoline[h]	A (450 g.)	...	230; 248	1/4.5	91
Carbazole	A (200 g.)	640	275; 282	7.5/>11[i]	70[i]
Phenothiazine	A (150 g.)	600	260; 276	24/48	48

[a] Procedure A involved use of the amount of clay plate indicated in the parentheses; procedure B involved no clay plate. [b] Millimoles of amine; a 10–15% excess of ester was taken unless otherwise is stated. [c] Alkali-soluble, acid-insoluble, ester-free material. In the cases of the arylalkylamines (lines 1–6) the crude materials were relatively pure, the phenothiazine products characteristically melted about 20–30° too low at this point, and the carbazole product about 10° low. [d] Run simultaneously with the run listed on the preceding line. Both runs went at essentially the same rate. This compound previously reported in D.R.P. No. 490274 [*cf. Chem. Zentr.*, **I**, 2632 (1930)]. [e] Product: 1-propyl-3-ethyl-4-hydroxy-2-quinolone, m.p. (from ethanol–water) 191–194°. *Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.81; H, 7.22. [f] Product: 1-isopropyl-3-ethyl-4-hydroxy-2-quinolone, m.p. (from ethanol–water) 131–132°. *Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 73.07; H, 7.36. [g] Product: 4,6-diketo-5-ethyllilolidine or 5-ethyl-6-hydroxy-1,2-dihydro-4H-pyrrolo[3,2,1-*ij*]-quinolin-4-one, m.p. (from much ethanol) 282–285°. *Anal.* Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.36; H, 6.01. [h] Product: 2-methyl-4,6-diketo-5-ethyllilolidine or 2-methyl-5-ethyl-6-hydroxy-1,2-dihydro-4H-pyrrolo[3,2,1-*ij*]-quinolin-4-one, m.p. (from ethanol) 222–223°. *Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.60. Found: C, 73.58; H, 7.10. [i] Stopped before completion as the reaction mixture had solidified. Product previously reported in ref. 4a.

of an amide-ester such as IIa (or of some equivalent) to I. When phenothiazine and a 10% excess of diethyl ethylmalonate were heated in the presence of clay plate until *one* mole of ethanol was evolved per mole of phenothiazine taken, and the reaction was worked up, the following were obtained (all in moles per mole of phenothiazine taken): recovered diethyl ethylmalonate, 0.464; recovered phenothiazine, 0.414 (isolated by crystallization and/or high-vacuum sublimation) + 0.10 (this is probably phenothiazine; however, it was not isolated and characterized as such, but was identified by vapor phase chromatography among the higher melting fractions obtained by chromatography on Woelm neutral alumina of a benzene–hexane solution of the otherwise uncharacterized fractions); "ethylmalonylphenothiazine": 0.282. Thus, even ignoring the phenothiazine and ester that have gone into the tars and other side reaction products, not over 29% of the phenothiazine or 35% of the diethyl ethylmalonate are unaccounted for and represent the maximum amount of half-ester half-amide IIa (or of bisamide IId) which might be present[12] at the point at which half of the theoretical amount of ethanol had been evolved.

It is therefore obvious that, at least for this pair of reactants, the rate of step *a* is much slower than that of the cyclization step (and of any other steps, *e.g.*, possibly formation of IId, which might be between step *a* and the cyclization). Since step *a* cannot be reversible because ethanol is distilled, it is rate-determining.

Three factors would be anticipated to influence the rate of step *a*. The first of these would be the nucleophilic character of the nitrogen, which might be approximated for present purposes by the (proton) base strength of the amine reactant. A second factor would be the nature of the alcohol moiety of the malonic ester. Thus, aryl esters undergo bimolecular displacements at the ester carbonyl far more rapidly than do esters of aliphatic alcohols, both by acid-catalyzed and base-catalyzed reactions. A third factor would be steric. A very crude attempt to assess these factors can be obtained from Table I, which gives the temperature at which ethanol was evolved at a useful rate during typical cyclizations of various amines with diethyl ethylmalonate. The time for evolution of half of the theoretical amount of ethanol is also given as a rough measure of reaction rate.

As has been indicated above, comparisons of lines 1–6 of Table I with lines 7 and 8 clearly show the greater ease of reaction of the alkylanilines, as compared with the less basic diarylamines. This anticipated difference seems real, although significance should not be read into the small differences between the apparent rates of individual amines within the two groups.

The effect of using a better leaving group than ethoxyl has been shown in work recently reported,[13] in which the bis(2,4-dichlorophenyl) ester of benzylmalonic acid was found to react rapidly and in good yield (without clay plate) with several heterocyclic compounds, including phenothiazine. Use of an ester of this sort might well be advantageous, especially in cases where the parent malonic acid is difficultly come by, or if the arylamine were unstable to prolonged heating, but this procedure

(12) Actually, the ratio of "ethylmalonylphenothiazine" isolated to phenothiazine unaccounted for, 47%, is not too far off from the yields obtained in preparative runs of this size. This makes an even stronger case for the argument about non-accumulation of intermediates.

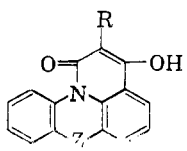
(13) E. Ziegler, H. Junek, and U. Rossmann, *Monatsh. Chem.*, **92**, 809 (1961); E. Ziegler, H. Junek, E. Nölken, K. Gelfert, and R. Salvador, *ibid.*, **92**, 814 (1961).

does require that the bis(2,4-dichlorophenyl)-malonate be made, whereas the ethyl esters are commercially available in many cases, and readily prepared by methods in the literature in most cases. Interestingly enough, the aryl ester method is reported to give better yields (90%) of "benzylmalonylphenothiazine" than the yields of "ethylmalonylphenothiazine" obtained by us (45–55%) using the clay plate catalyst and ethyl ester, but conversely, we got a better yield of "ethylmalonylphenoxazine" (90%) than is reported by the aryl ester method for "benzylmalonylphenoxazine" (47%).

The effect of a moderate amount of steric hindrance in the amine reactant is found to be negligible under the very crude conditions of our measurements. It is obvious from the table that the rates of the reactions of methylaniline, of propylaniline, and of isopropylaniline with the same malonic ester are roughly comparable. N-Triphenylmethylaniline reacted more slowly, but the acidic product was a low yield of 2,4-dihydroxy-3-ethylquinoline, *i.e.*, loss of trityl group had occurred, thus any comparison involving this substance would be invalid.

As would be anticipated, additional substitution at the α-carbon of the malonic ester reactant appears, from one trial of diethyl ethylbutylmalonate and phenothiazine, to be far more effective than substitution at nitrogen at slowing reaction, since evolution of half of the theoretical amount of ethanol took 34 hours, even at a bath temperature of 300°.

In addition to the compounds already mentioned, necessary details of the method of synthesis, physical properties, and analytical data for the phenothiazines, "methylmalonylphenothiazine" (IIIa), "propylmalonylphenothiazine" (IIIb), "butylmalonylphenothiazine" (IIIc), and "phenylmalonylphenothiazine" (IIId), and for the phenoxazines, "methylmalonylphenoxazine" (IIIe) and "ethylmalonylphenoxazine" (IIIf), are given in the Experimental. The analogous data for the new compounds in Table I are given as footnotes to that table.



Phenothiazines, Z = S
IIIa. R = CH_3
IIIb. R = n-C_3H_7
IIIc. R = n-C_4H_9
IIId. R = C_6H_5

Phenoxazines, Z = O
IIIe. R = CH_3
IIIf. R = C_2H_5

Certain unsuccessful attempts at syntheses of specific compounds are of interest, even though most represent single attempts. Ziegler, *et al.*,[13] have already reported the cyclization of malonic acid with phenothiazine in the presence of phosphorus oxychloride, to give "malonylphenothiazine," although in poor yield. We had unsuccessfully attempted an analogous cyclization of phenothiazine and isopropylidine malonate[14] in the presence of a catalytic amount of phosphorus oxychloride, tried in the hope that acetone would be a superior leaving group. The fusion with sulfur in the presence of aluminum chloride of the readily prepared 1-phenyl-4-hydroxy-2-quinolone ("malonyldiphenylamine"[15]) was also tried. This gave copious evolution of hydrogen sulfide, but little base-soluble product. We also attempted the "uncatalyzed" reaction of malonyl chloride (with a little malonyl bromide[16]) and phenothiazine in dioxane, which gave, after a day on the steam bath followed by addition of ethanol, no "malonylphenothiazine." The only base-soluble product had a melting point identical to that of 2-carbethoxyacetophenothiazinylamide, *i.e.*, the unethylated analog of compound IIa, but was not investigated further. Other reactions which gave no separable base-soluble products, despite copious evolution of ethanol during the heating period, were high temperature reactions of phenothiazine with diethyl dimethylaminoethylmalonate, and of leuco-methylene blue with diethyl ethylmalonate, both in the presence and the absence of clay plate. Attempted reaction of tricarbethoxymethane with phenothiazine gave little base-soluble product.

Experimental

1-Keto-2-ethyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound I) ("Ethylmalonylphenothiazine"[5]) by the Thermal Method.—A mixture of 100 g. (0.5 mole) of phenothiazine, 103.4 g. (0.55 mole) of diethyl ethylmalonate, and one clay plate (158 g.) broken into pieces smaller than 0.5 cm. in their longest dimensions, was heated in a flask surmounted by an unpacked column about 20 cm. high. The bath temperature was such that ethanol vapor was produced at a rate sufficient to keep a thermometer atop the column at 77–78° (bath temperature 261° during evolution of nearly all of the first half mole of ethanol, and 273° during evolution of the second half mole). After having been heated for 19 hr., the reaction mixture was cooled somewhat and poured, while still hot enough to be fluid, into 1100 ml. of 1 *N* aqueous sodium hydroxide solution. It was then heated on the steam bath for 5 hr., cooled, and extracted with benzene twice. The turbid aqueous solution was filtered through a Büchner funnel with the help of a filter-aid, and brought to pH 6 with 6 *N* hydrochloric acid. The resulting precipitate, washed with water, and dried, weighed 78 g. (53%) and had m.p. 190–192°. It could be recrystallized from ethanol–water, giving 57% recovery in two crops melting 207–213°. Several additional recrystallizations gave a product of m.p. 223–224°, but material melting over 205° was satisfactory for synthetic purposes.

Omission of the clay plate led to yields of 10% to 25%

(14) D. Davidson and S. A. Bernhard, *J. Am. Chem. Soc.*, **70**, 3426 (1948).
(15) C. G. Vogt and C. G. Verdery, British Patent 623,323 (1949).
(16) W. Treibs and B. Streckenbach, *Chem. Ber.*, **94**, 1734 (1961).

in runs of the same size, and to no detectable product in one run using 450 g. of phenothiazine. The theoretical amount of ethanol was evolved, although more slowly than with clay plate present. A single preparation using twice as much clay plate gave essentially the same yield of product, with approximately the same rate of ethanol evolution at the same bath temperature.

10-(2-Carbethoxybutyroyl)phenothiazine (Compound Ia).—A solution of 41 g. (0.206 mole) of phenothiazine in 400 ml. of dried benzene was stirred as 36.7 g. (0.206 mole) of 2-carbethoxybutyroyl chloride in 50 ml. of dried benzene was added dropwise. The solution was then heated under reflux until the evolution of hydrogen chloride stopped (28 hr.). The benzene was distilled at the water pump, leaving 74 g. of a greenish oil. A small portion of this was taken up in ether, extracted successively with water and aqueous sodium carbonate solution. Evaporation of the ether left an oil which solidified when refrigerated in hexane solution, and had m.p. 88–89° after recrystallization from benzene–hexane.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61. Found: C, 66.75; H, 5.63.

10-(2-Carboxybutyroyl)phenothiazine (Compound Ib).—The bulk of the above 74 g. of oil was taken up in 500 ml. of ether, filtered from a little dark, insoluble floc, and let stand for 4 hr. at room temperature with a solution of 11.2 g. (0.206 mole) of potassium hydroxide in absolute ethanol. The resulting light grey potassium salt of Ib was filtered off, and combined with an additional 13.3 g. of precipitate obtained by addition of an equal volume of ether to the filtrate. The resulting 60 g. of salt was dissolved in water, filtered with a filter-aid, and the acid precipitated with 6 *N* hydrochloric acid. This gave 34.6 g., m.p. 145–147° dec. This was recrystallized twice from acetone–hexane to give 21 g. in two crops, m.p. 151–152° dec.

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.15; H, 4.83. Found: C, 65.64; H, 5.21.

"Ethylmalonylphenothiazine" by Cyclization of 10-(2-Chlorocarbonylbutyroyl)phenothiazine (Compound IIc).—The acid chloride was prepared from 21.5 g. (0.069 mole if pure) of 10-(2-carboxybutyroyl)phenothiazine dissolved in 50 ml. of dried benzene, by addition of 15 ml. of thionyl chloride, followed by 1 hr. of heating under reflux. The residue after removal of benzene and thionyl chloride on the steam bath at 10-mm. pressure was 23.5 g. of a green-blue oil, not further characterized, but immediately dissolved in 70 ml. of carbon disulfide. This solution was treated with a single portion of 9.4 g. (1.01 equivalents) of powdered aluminum chloride, stirred 0.5 hr. until the spontaneous warming stopped, and then heated under reflux an additional 20 min. It was then poured into 500 g. of ice holding 15 ml. of hydrochloric acid. The resulting 21 g. of yellow solid was treated with aqueous sodium carbonate solution, filtered from 1.5 g. of residue, and acidified, giving 14.9 g. (73%), m.p. 200–206°. This was recrystallized from ethanol–water, and then had the correct melting point and mixed melting point with "ethylmalonylphenothiazine" (I) prepared by the high temperature reaction of diethyl ethylmalonate and phenothiazine as described above. Products of the two routes also had identical infrared absorption spectra.

1-Keto-2-methyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound IIIa) ("Methylmalonylphenothiazine").—This was prepared from 195 g. (0.98 mole) of phenothiazine, 210 g. (1.08 moles) of diethyl methylmalonate, and 310 g. of clay plate fragments, heated analogously for 44 hr. first at 240°, then at 255° bath temperature. The reaction became a solid mass even at these temperatures, and so had to be dissolved out of the reaction vessel by digestion with 3 l. of 0.6 *N* sodium hydroxide solution. Filtration and precipitation by acid gave 134 g. (48% if it were pure) of a precipitate best filtered and washed with water after "digestion" on the steam bath with the supernatant liquid for several hours. The resulting yellow solid had m.p. 245–261°. It could be recrystallized poorly from pyridine–benzene–ether, *n*-butyl alcohol, or much acetic acid, then having m.p. 289–294°.

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.35; H, 3.94. Found: C, 68.30; H, 4.04.

Use of half of the above proportions of phenothiazine and ester with 60 g. of clay plate sieved to pass through a No. 20 mesh sieve, and stirring of the reaction mixture at bath temperature 266° for 23 hr., then for 14 hr. at 275° led to a 53% yield of product of m.p. 255–276°.

1-Keto-2-propyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound IIIb) ("Propylmalonylphenothiazine").—This was prepared using powdered clay plate at bath temperature 275–284° giving a crude product of m.p. 140–180° in 55% of the calculated amount. This, after one recrystallization from ethanol–water and two from ethyl acetate, had m.p. 214–217.5°. Recovery of pure material was poor and variable.

Anal. Calcd. for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89. Found: C, 69.89; H, 5.08.

1-Keto-2-butyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound IIIc) ("Butylmalonylphenothiazine").—From 80 g. of phenothiazine, 100 g. of diethyl butylmalonate, and 300 g. of clay plate fragments heated at bath temperature 277° for 22 hr., 98 g. (73%) of a crude product was obtained. This could be recrystallized from much heptane or from ethyl acetate–hexane, and then had m.p. 128–135°. It was freed of solvent for analysis with great difficulty requiring 2 days at 80° at a pressure of 0.01 mm. before it was free of ethyl acetate, and gave a satisfactory analysis.

Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.80; H, 5.68; N, 4.09 (Kjeldahl); 4.08 (Dumas).

1-Keto-2-phenyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound IIId) ("Phenylmalonylphenothiazine").—Preparation of this compound had to be carried out at a higher temperature than the aliphatic esters required for ethanol evolution at a comparable rate. Indeed, heating was stopped after 6 hr. at 296° bath temperature (internal temperature 277°) followed by 0.5 hr. at 305°, even though only 67% of the theoretical amount of ethanol had been obtained. The resulting mass was partitioned between benzene and 1 *N* aqueous sodium hydroxide. Precipitation of the filtered aqueous layer with 6 *N* hydrochloric acid gave 40% of theoretical yield of a yellow solid of m.p. 250–260°. This was washed with acetone, and recrystallized from 2-butanone four times, m.p. 280–282°.

Anal. Calcd. for $C_{21}H_{13}NO_2S$: C, 73.45; H, 3.81; N, 4.08. Found: C, 72.96; H, 4.04; N, 4.20 (Dumas).

1-Keto-2-methyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenoxazine (Compound IIIe) ("Methylmalonylphenoxazine").—A mixture of 183 g. (1 mole) of phenoxazine, 183 g. of diethyl methylmalonate, and 150 g. of clay plate fragments heated in the same way as the foregoing at 265° bath temperature solidified when about half of the theoretical amount of ethanol had been evolved. It was then heated at bath temperature 285° till the theoretical amount of ethanol had been evolved. The crude material was dissolved out of the reaction vessel with hot pyridine (*ca.* 1.5 l.) and recrystallized directly from pyridine–water. The resulting crystals had the same melting point as the material obtained by acidifying the mother liquors, 278–288°. Recrystallization of the combined solids so obtained in 69% yield, first from 2-butanone and then from acetic acid, gave a yellow solid of m.p. 284–295°.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18. Found: C, 72.81; H, 4.24.

1-Keto-2-ethyl-3-hydroxy-1H-pyrido[3,2,1-*kl*]phenoxazine (Compound IIIf) ("Ethylmalonylphenoxazine").—This was obtained analogously in 91% yield without any crystalliza-

tion at the mid-point of ethanol evolution, when 50 g. of phenoxazine, 65 g. of diethyl ethylmalonate, and 20 g. of clay plate chips were heated at 270–280° for 16 hr. The crude material obtained by precipitation from aqueous sodium hydroxide solution, which had m.p. 200–216°, melted at 222–226° after two recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.15; H, 4.69. Found: C, 73.10; H, 4.22.

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The Semmler–Wolff Aromatization and Beckmann Rearrangement of 2-[β-(2- and 4-Pyridyl)ethyl]-1-tetralone Oximes[1]

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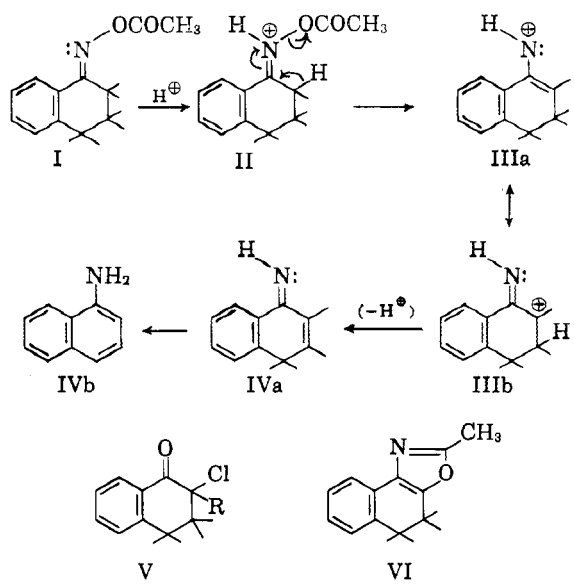
Treatment of the oximes mentioned in the title with acetic anhydride in acetic acid and hydrogen chloride afforded a mixture of 2-[β-(2- and 4-pyridyl)ethyl]-1-naphthylamines and 6-[β-(2- and 4-pyridyl)ethyl]-2,3-benzocaprolactams. The latter arise during a Beckmann rearrangement of these oximes which involves alkyl group migration. The isomeric 2-[β-(2- and 4-pyridyl)ethyl]-5,6-benzocaprolactams were made by the conventional Beckmann rearrangement of the oximes with polyphosphoric acid (phosphorus pentoxide in phosphoric acid), in which aryl migration occurred.

The aromatization of cyclohexenones oximes to the corresponding anilines by a variety of acidic reagents was first described by Semmler[2] and found by Wolff[3] to be a general reaction.[4,5] The most effective reagent for this reaction has been found to be "Beckmann's mixture" which consists of a mixture of acetic anhydride in acetic acid saturated with hydrogen chloride. In this acidic medium, the Beckmann rearrangement of the oxime must be considered a possible competing reaction. However, judging from the examples in the literature,[4,5] in Beckmann's mixture, cyclohexenone oximes are preferentially aromatized rather than rearranged. Ostensibly, in Beckmann's mixture, the oximes form the O-acetyl derivatives first which then lose the elements of acetic acid and water to form the corresponding anilines.

Mechanisms of this reaction have been advanced for the aromatization of 1-tetralone oximes[5–7] and the one suggested by Vorozhtsov and Koptiug[5] is presented. From the reaction of O-acetyl 1-tetralone oxime, I, with hydrogen chloride in acetic acid they isolated 1-naphthylamine, IVb (as the hydrochloride, 31%), 1-acetamidonaphthalene (3.3%), 2-chloro-1-tetralone, V(R = H), (2%) and the oxazole derivative, VI, (8.6%). They postulated the formation of all of their products *via one* common intermediate and proposed the following reaction path: Protonation of I on nitrogen leads to II which loses acetic acid to form the enamine, represented by the resonance hybrids IIIa and IIIb. From this reactive intermediate they accounted for all of their products in the following manner:



Loss of a proton from the enamine leads to IVa which tautomerizes to 1-naphthylamine, IVb; attack of a chloride ion at the carbonium ion center of IIIb would yield 2-chloro-1-tetralone imine which would hydrolyze (during the reaction or work-up) to form the ketone V (R = H); similarly, attack of acetate ion on IIIb would form 2-acetoxy-1-tetralone imine which could cyclize with the loss of water to yield VI. These workers did not isolate any lactams due to a Beckmann rearrangement of 1-tetralone oxime.

We studied the action of hydrogen chloride on 2-[β-(2- and 4-pyridyl)ethyl]-1-tetralone oximes in acetic anhydride and acetic acid solution. In

(1) A portion of this study was taken from the thesis submitted by Richard E. Hewitson as partial fulfillment for the Master of Science degree, University of Illinois, Chicago, Illinois, June, 1962.

(2) F. W. Semmler, *Ber.*, **25**, 3352 (1892).

(3) L. Wolff, *Ann.*, **322**, 351 (1902).

(4) For examples, see the review of the Beckmann Rearrangement by L. G. Donaruma and W. Z. Heldt, "Organic Reactions," Vol. 11, J. Wiley & Sons, Inc., New York, N. Y., 1960, p. 30.

(5) N. N. Vorozhtsov and V. A. Koptiug, *J. Gen. Chem. U.S.S.R.* (Eng. Transl.), **28**, 1697 (1958), have also summarized the field.

(6) A. Hardy, E. R. Ward, and L. A. Day, *J. Chem. Soc.*, 1979 (1956).

(7) M. V. Bhatt, *Experientia*, **13**, 70 (1957).