[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF HARVARD UNIVERSITY]

Picrotoxin. I. The Skeleton of Picrotoxinin. The Degradation to Picrotoxadiene

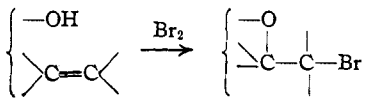
BY HAROLD CONROY[1]

Picrotoxinide, a new transformation product of picrotoxinin, has been degraded by a stepwise procedure to a bicyclic, doubly unsaturated hydrocarbon, picrotoxadiene, which retains intact the important features of the picrotoxinin skeleton. Previous structural inferences are discussed in the light of infrared spectral data on the picrotoxin family.

Picrotoxin, first isolated by Boullay[2] in 1812, is a typical representative of the class of amaroids, or non-nitrogenous bitter principles. It can be obtained from the fruit of the shrubs *Cocculus indicus* and *Anamirta cocculus*, and it has a very powerful physiological action. Nearly 70 years after the original isolation, picrotoxin was shown[3] to be composed of two substances, picrotoxinin, $C_{15}H_{16}O_6$, and picrotin, $C_{15}H_{18}O_7$, which can be readily separated only by chemical means.[4,5] No satisfactory structure has been proposed for either of these compounds.

Picrotoxinin and picrotin have long been suspected to be dilactones,[6] although it has been implied by Sutter and Schlittler[7] that there is present just one "normal" lactone system. The infrared spectra (Fig. 1, curves 1 and 2) strongly suggest that the compounds possess two lactone rings, both probably five-membered, for in each case the only carbonyl absorption is a double peak with characteristic maxima[8] at 5.57 and 5.63 μ. Picrotoxinin is known to possess a single double bond from the combined results of bromination,[4,5] hydrogenation[9,10] and ozonization[9,11] experiments; this conclusion is substantiated by the presence of a weak band at 6.04 μ in the infrared spectrum. Picrotin is saturated. Neither substance gives any carbonyl derivatives,[4] and it has been suggested[9] from the results of the Zerevitinov determination[12] that there is present in picrotoxinin a single hydroxyl group and in picrotin two hydroxyl functions. The disposition of the single oxygen remaining in each case lacks proof, but it has been assumed[9] to be present as an ether linkage.

On bromination picrotoxinin provides two sparingly soluble, stereoisomeric monobromo derivatives,[4,5] $C_{15}H_{15}O_6Br$, while picrotin does not react; this reaction is the basis of separation of the components present in the original amaroid. On debromination with zinc[5] these derivatives[13] are quantitatively converted back to picrotoxinin. The hydroxyl absorption (2.90 μ) in the spectrum of picrotoxinin is not present in that (Fig. 1, curve 3) of $\alpha\beta$-bromopicrotoxinin, consequently the bromination must involve participation of the hydroxyl group, as shown, a hypothesis which is supported by the results of the Zerevitinov determinations and originally suggested by Robertson, *et al.*[10] These conclusions require that the hydroxyl group be located close in space to the double bond and provide additional encouragement for the assumption that the sixth oxygen atom in picrotoxinin is present as an ether linkage and not as a second hydroxyl group.[14]



If picrotoxinin be treated with one equivalent of methanolic alkali, the main product is the methyl ester of the monobasic picrotoxic acid,[6] $C_{15}H_{18}O_7$. This acid can also be obtained[6] by the action of hot dilute sulfuric acid upon picrotoxinin. The infrared spectrum (Fig. 1, curve 4) of the ester retains the band at 5.57 μ and so it is logical to assume that the lactone ring responsible for absorption at 5.63 μ has been opened. On the other hand, $\alpha\beta$-bromopicrotoxinin with base gives $\alpha\beta$-bromopicrotoxininic acid, which can be debrominated to α-picrotoxininic acid,[15] also $C_{15}H_{18}O_7$ and monobasic. Remarkably enough, it appears that one of the original lactonic systems present in picrotoxinin has been converted to a free carboxyl group and the other to a new and different lactone in $\alpha\beta$-bromopicrotoxininic acid and α-picrotoxininic acid, for neither of the lactone bands of picrotoxinin are exhibited by these acids. The spectrum (Fig. 2, curve 5) of the bromo-acid shows a single broad band in the neighborhood of 5.8 μ, and that of its sodium salt (Fig. 2, curve 6) retains a lactone peak at 5.75 μ in addition to the broad intense band at 6.25μ due to the carboxylate anion. Similarly the spectrum (Fig. 2, curve 7) of α-picrotoxininic acid possesses a broad band at 5.75 μ just resolved (by the Baird instrument) into two peaks at 5.70 and 5.78 μ. The newly created bromo-ether system in

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(2) P. F. G. Boullay, *B. Pharm.*, **4**, 367 (1812).

(3) L. Barth and M. Kretschy, *Monatsh.*, **1**, 99 (1881); **2**, 796 (1881); **5**, 65 (1884); E. Paterno and A. Oglialoro, *Gazz. chim. ital.*, **6**, 531 (1876); **7**, 193 (1877); **11**, 36 (1881).

(4) R. J. Meyer and P. Bruger, *Ber.*, **31**, 2958 (1898).

(5) P. Horrmann, *ibid.*, **45**, 2090 (1912).

(6) P. Horrmann, *Ann.*, **411**, 273 (1916).

(7) M. Sutter and E. Schlittler, *Helv. Chim. Acta*, **33**, 902 (1950).

(8) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1076 (1949).

(9) D. Mercer and A. Robertson, *J. Chem. Soc.*, 288 (1936).

(10) R. W. H. O'Donnel, A. Robertson and J. C. Harland, *ibid.*, 1261 (1939).

(11) P. Horrmann and H. Wachter, *Ber.*, **49**, 1554 (1916).

(12) See ref. 6. The Zerevitinov determination generally gives poor results throughout the picrotoxin series. For example picrotoxinin indicates 1.5 active hydrogen atoms; the bromopicrotoxinins show 0.3 active hydrogen. This phenomenon is ascribed by Mercer and Robertson (ref. 9) to incomplete removal of crystal water, held tenaciously by these compounds, although a Zerevitinov determination on fully dried material is not reported.

(13) The mixture of the two bromo derivatives produced in the bromination reaction is here designated by the prefix "$\alpha\beta$."

(14) The introduction of the bromine atom into the molecule can hardly involve more than one hydroxyl group, and consequently since the bromo derivative definitely possesses no hydroxyl, picrotoxinin must have only one. This conclusion, taken with the occurrence of only two carbonyl (lactone) bands in the infrared spectra and the lack of carbonyl reactivity, strongly suggests that the sixth oxygen is an ether linkage.

(15) P. Horrmann, *Ber.*, **46**, 2793 (1913).

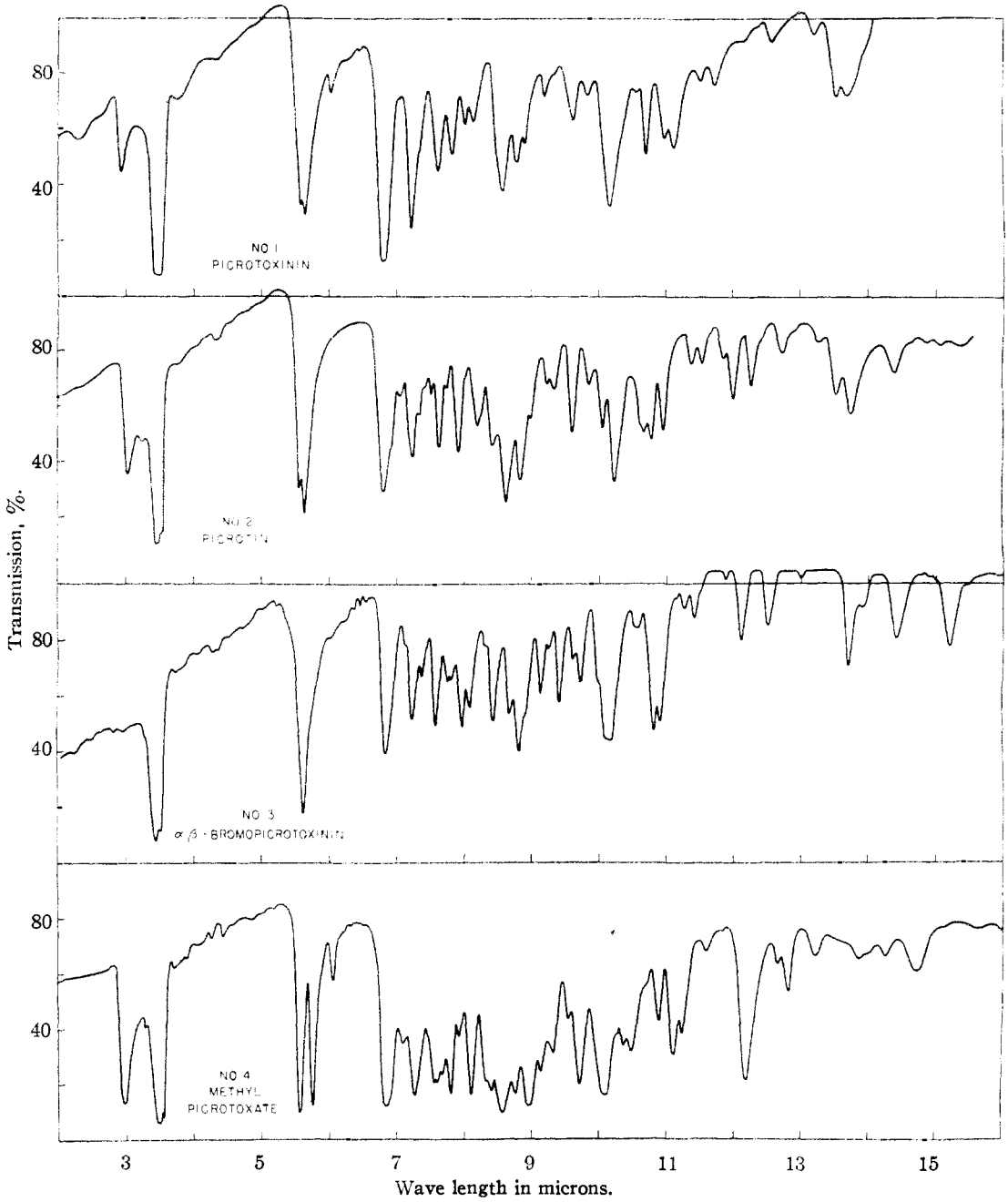
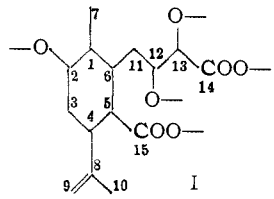


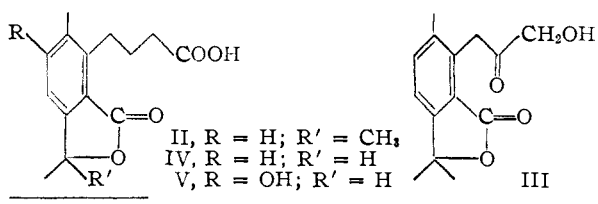
Fig. 1.—Infrared spectra in nujol.

the bromopicrotoxinins profoundly affects the course of the attack of base upon the molecule.

The partial carbon skeleton depicted in the expression (I) has been proposed by Robertson, *et al.*,[16,17] in order to account for the formation of the substances picrotic acid (II) and picrotonol (III), first obtained by Angelico[18] and Oglialoro[19] in the acid-catalyzed aromatization reactions of picrotoxinin. The position of the double bond in I was deduced from the several facts: (1) upon ozonization[11] of picrotoxinin a ketone, picrotoxinone, $C_{14}H_{14}O_7$, and formaldehyde are produced, and (2)



I



III

(16) J. C. Harland and A. Robertson, *J. Chem. Soc.*, 937 (1939).
(17) D. Mercer, A. Robertson and R. S. Cahn, *ibid.*, 997 (1935).
(18) F. Angelico, *Gazz. chim. ital.*, **41**, ii, 337 (1911).
(19) A. Oglialoro, *ibid.*, **21**, ii, 213 (1891).

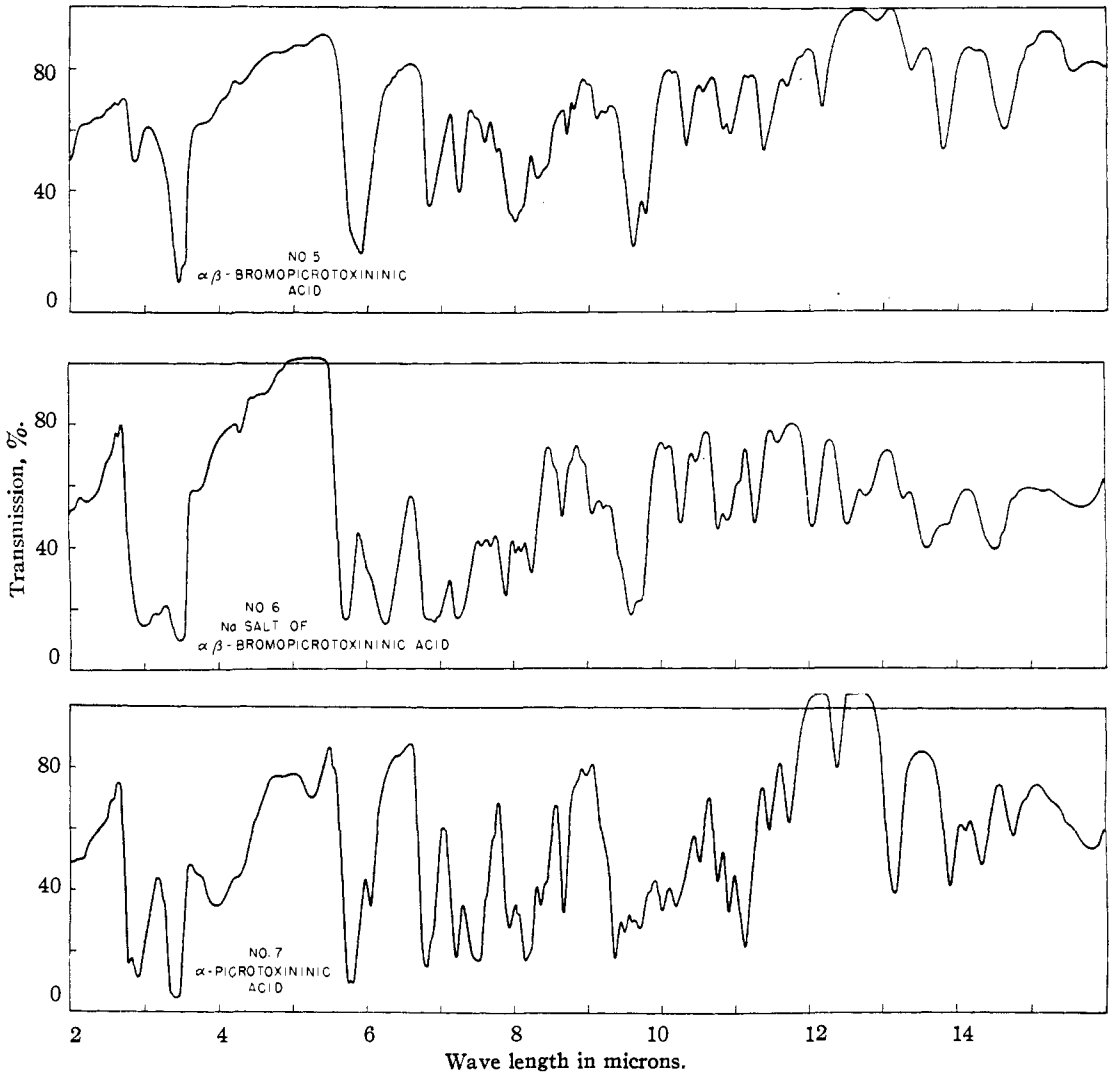
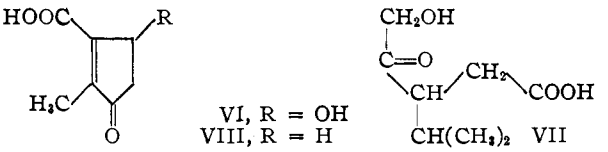


Fig. 2.—Infrared spectra in nujol.

picrotoxinone with red phosphorus and hydriodic acid gives nor-picrotic acid (IV) hydroxy nor-picrotic acid (V) and a phenolic ketone, $C_{13}H_{16}O_2$.[16] These degradation products further allowed Robertson, *et al.*, to place the oxygen atoms attached to carbons 2, 12, 13, 14 and 15 shown in the skeleton (I).

However, it was observed by these authors that the skeleton of (I) lacked one additional carbon–carbon bond, *i.e.*, two carbocyclic rings must be present. This follows directly from the empirical formula if provision be made for two lactones, one carbon–carbon double bond and one oxide ring; it follows indirectly from the formation of the ketonic function at C-12 in picrotonol where none had previously been present. The obvious possibility, pointed out by Robertson, is that this missing bond involves C-12, and that when it is broken by aromatization of the six-membered ring a ketone carbonyl is produced at the site of cleavage. It is noted here, however, that this hypothesis applies equally to a bond to C-13, for in the same manner of cleavage an α-hydroxy aldehyde could be formed, which, under the conditions of the reaction might be expected to tautomerize to picrotonol.

More recently, Sutter and Schlittler[7,20] found that α-dihydropicrotoxinin on heating with aqueous bases gave the substances (VI), (VII) and (VIII), although they made no attempt to interpret these products in terms of the general structural picture.



Despite the fact that other hypotheses cannot be rigorously excluded at this point, two particularly acceptable interpretations of these facts are obtained if additional oxygen atoms are shown attached to C-3 and C-6, and if the missing bond be drawn from C-13 either to C-1 or to C-5, as in the structures (IX) and (X). In the case of IX, dealdolization with resultant cleavage between C-6 and C-5, then between C-2 and C-1, followed by β-elimination of the C-13 oxygen leads directly to two of the observed products, (VI) and (VII). On the other hand, the same two fragments could be

(20) M. Sutter and E. Schlittler, *Helv. Chim. Acta*, **30**, 403 (1947); **30**, 2102 (1947); **32**, 1855 (1949); **32**, 1860 (1949).

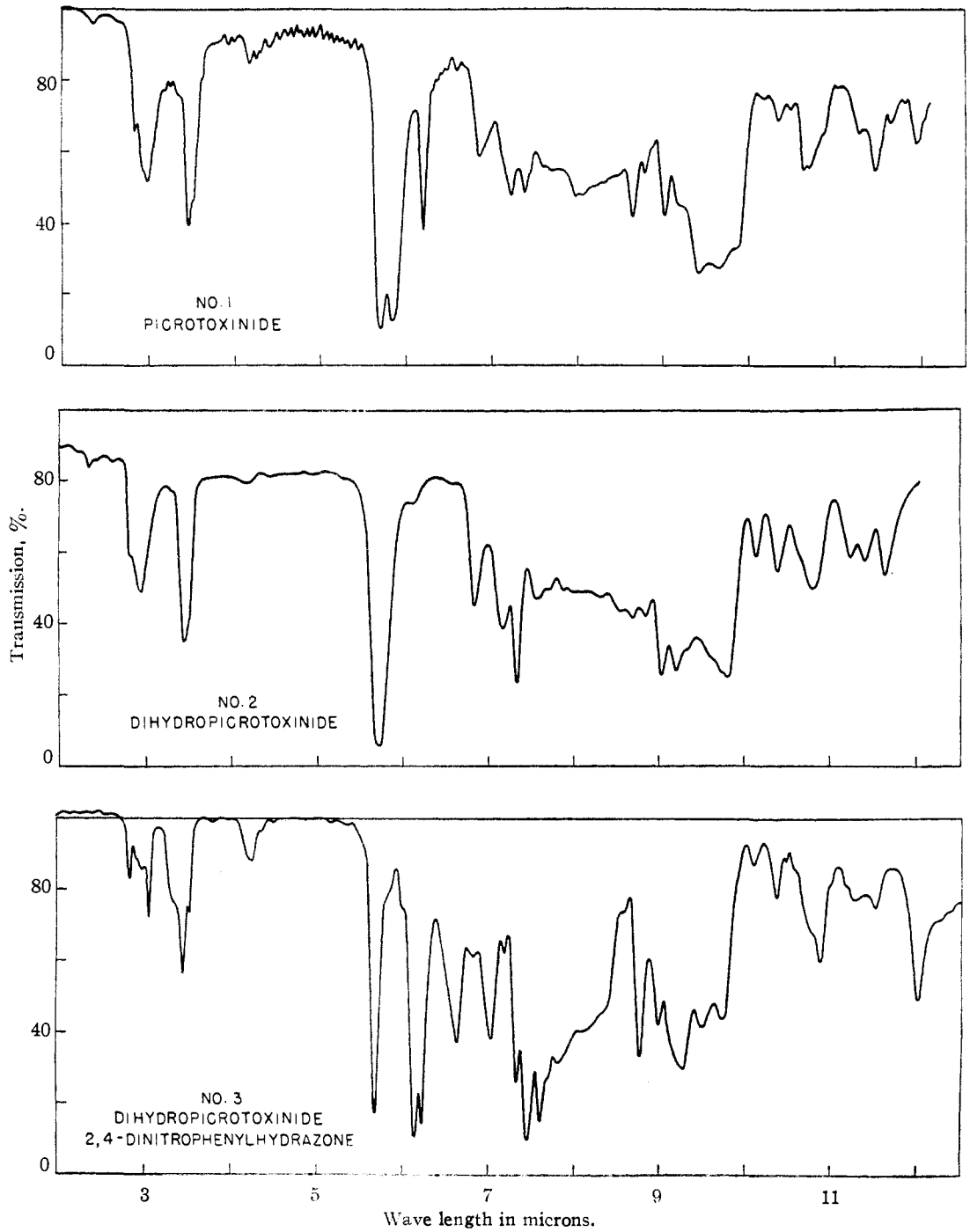
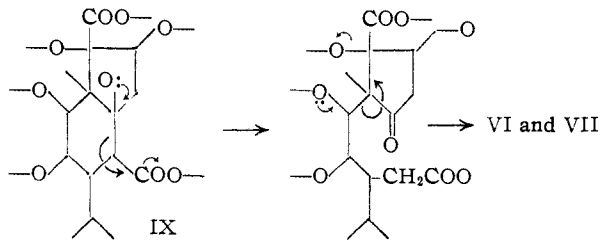
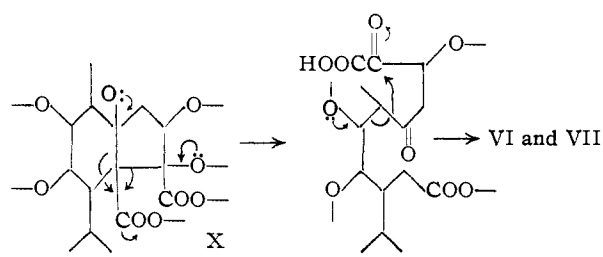


Fig. 3.—Infrared spectra in chloroform.



formed from X through the combined agencies of triple dealdolization and recyclization, as shown.

It is further observed that both of these partial structures (IX) and (X) are formally capable of yielding the aromatization products picrotic acid (II) and picrotonol (III); the discussion of possible reaction paths will be reserved at present.



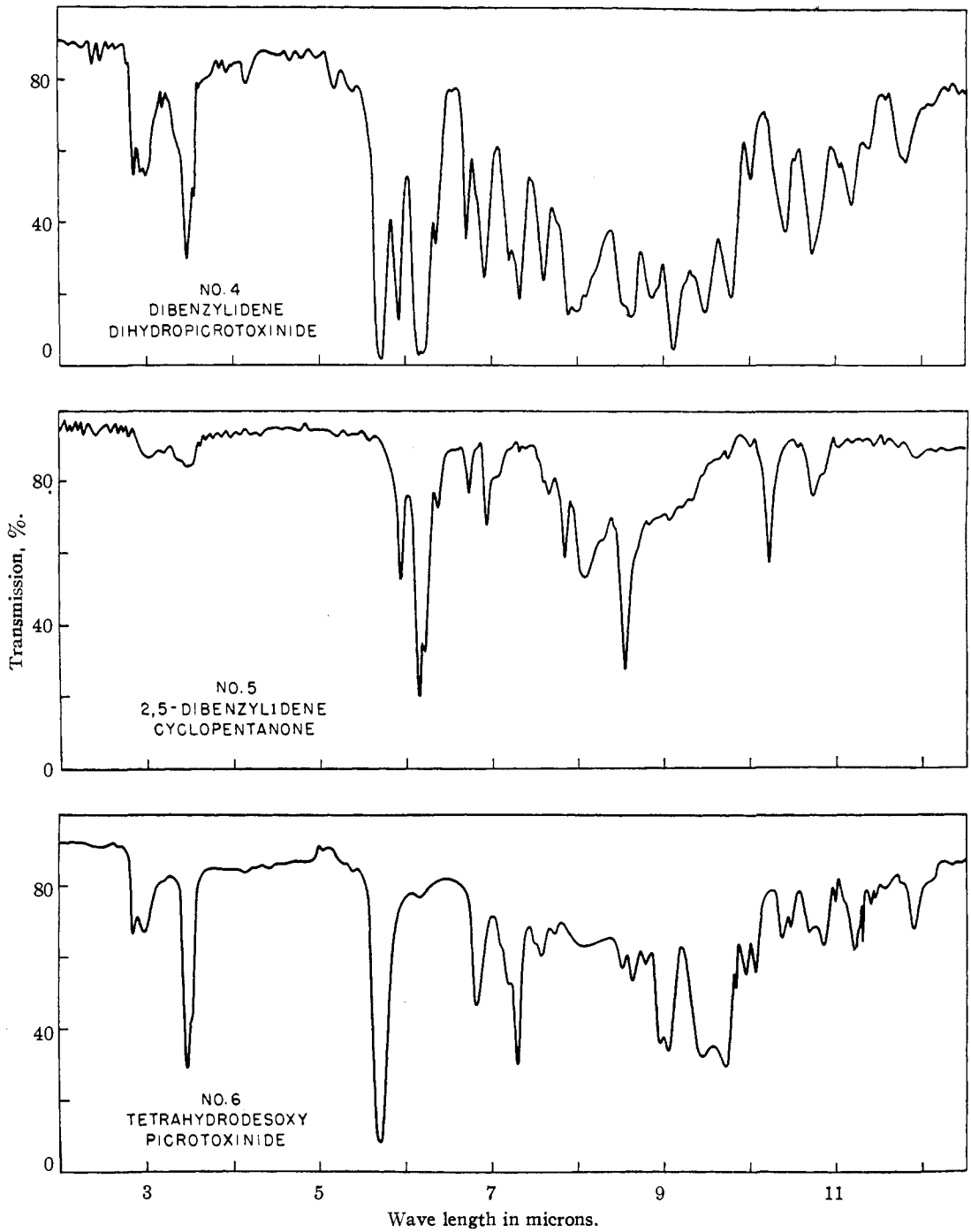


Fig. 4.—Infrared spectra in chloroform.

It seemed that positive proof of the location of the missing bond would be best obtained from a systematic, stepwise degradation leading to a compound still retaining the essential features of the skeleton, but simple enough for direct comparison with a synthetic sample. Accordingly, this was undertaken, and is reported in detail below.[21]

When dihydro-α-picrotoxininic acid[15] (observed by Horrmann to melt with decomposition) was heated to its m.p. (*ca.* 230°), a very smooth reaction took place with the formation of carbon dioxide, water, and a new substance, named picrotoxinide, $C_{14}H_{18}O_4$. The infrared spectrum (Fig. 3, curve 1) of picrotoxinide shows hydroxyl absorption at 2.90 μ, two carbonyl bands at 5.70 and 5.84 μ, in addition to a somewhat shorter band at 6.20 μ, assigned to a conjugated carbon–carbon double bond. The ultraviolet spectrum shows high intensity absorption (λ_{max} 254 mμ, log E 4.0) suggesting an α,β-unsaturated ketone. A brick-red 2,4-dinitrophenylhydrazone was obtained. Picrotoxinide is not acidic but dissolves slowly in aqueous sodium hydroxide. On hydrogenation in methanol with platinum oxide catalyst one mole of hydrogen was

(21) First reported in a Communication to the Editor, H. Conroy, THIS JOURNAL, **73**, 1889 (1951).

absorbed rapidly and a saturated hydroxy-keto-lactone, dihydropicrotoxinide, was isolated in very good yield.

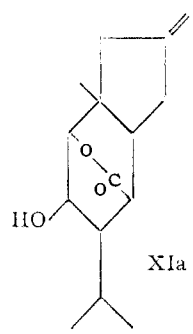
The infrared spectrum (Fig. 3, curve 2) of dihydropicrotoxinide shows a single broad carbonyl band at 5.73 μ, in addition to hydroxyl absorption at 2.90 μ, but there is no appreciable absorption in the 6.2 μ region. The ultraviolet spectrum indicates no high intensity maxima in the range of the Beckman instrument. The single carbonyl band in the infrared is actually the result of superposition of the two bands due to the lactone and the ketone functions, for the spectrum (Fig. 3, curve 3) of the (yellow) 2,4-dinitrophenylhydrazone still retains a sharp lactone peak at 5.70 μ. Clearly the shift in ketone carbonyl absorption from 5.84 μ in picrotoxinide to near 5.73 μ in the dihydro derivative, coupled with the disappearance of the C=C peak at 6.20 μ, requires that the change involved be that of reduction of the system $-\overset{|}{C}=\overset{|}{C}-CO-\overset{|}{C}-$ to $-\overset{|}{C}H-\overset{|}{C}H-CO-\overset{|}{C}-$. Further, the rather low[22] wave lengths of these ketone absorption bands strongly suggest that in picrotoxinide and its dihydro derivative *the ketonic function is contained in a five-membered ring.*

Dihydropicrotoxinide gave a dibenzylidene derivative with benzaldehyde in the presence of methanolic potassium hydroxide; this dibenzylidene compound is strikingly similar in its relevant physical properties (infrared, ultraviolet spectra) to 2,5-dibenzylidene cyclopentanone.[23] Thus the highly characteristic double bond region in the spectrum of dibenzylidenedihydropicrotoxinide (Fig. 4, curve 4) is exactly duplicated by the trace (Fig. 4, curve 5) of its simple analog, with, of course, the exception of the lactone peak at 5.70 μ. The ultraviolet maximum is at 344 mμ, log E 4.4, while 2,5-dibenzylidenecyclopentanone gives[24] $\lambda_{max.}$ 344 mμ, log E 4.44, to be compared with 2,6-dibenzylidene-3-methylcyclohexanone at $\lambda_{max.}$ 328 mμ, log E 4.54.

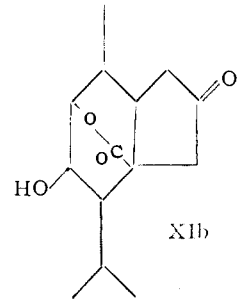
The formation of dibenzylidenedihydropicrotoxinide uniquely determines the position of the ketonic group upon the skeleton (I), *i.e.*, at C-12. No other position can be flanked by two methylene groups.[25]

When a solution of dihydropicrotoxinide in aqueous sodium hydroxide was acidified, a crystalline dihydroxy-keto-acid separated in good yield. The acid must possess a free 1,2-glycol system since it consumed one mole of periodate in methanolic aqueous solution, while the parent lactone did not react with periodate under these conditions, and consequently the structural unit $HO-\overset{|}{C}-\overset{|}{C}-O-CO-$ must be present in dihydropicrotoxinide. The parent lactone was quantitatively regenerated when the acid was heated to its m.p., about 200°.

At this stage it is clear that only two expressions (XIa and XIb) can be accepted for dihydropicrotoxinide.[26]

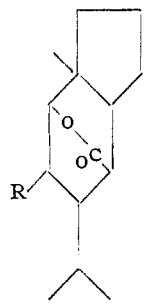


XIa

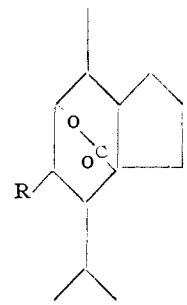


XIb

An excellent yield of the ethylenemercaptal of dihydropicrotoxinide was obtained with the use of ethane-1,2-dithiol in the presence of hydrogen chloride. Raney nickel desulfurization of the mercaptal according to the modified Mozingo method provided tetrahydrodesoxypicrotoxinide, $C_{14}H_{22}O_3$, (XIIa or XIIb) in good yield. The presence of the lactone bridge in the latter substance was demonstrated by its infrared peak at 5.70 μ (Fig. 4, curve 6), and by the fact that it dissolved slowly in aqueous sodium hydroxide. Again the corresponding dihydroxy-acid reacted with periodate in aqueous methanolic solution; one mole was



XIIa, R = OH
XIIIa, R = $OOCC_6H_5$



XIIb, R = OH
XIIIb, R = $OOCC_6H_5$

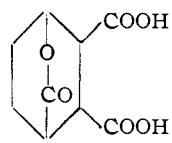
(22) Six-membered and acyclic $\alpha\beta$-unsaturated ketones generally absorb in the region 5.95–6.04 μ, while the corresponding saturated compounds give rise to bands close to 5.82 μ. On the other hand, conjugated cyclopentenones absorb at 5.83 μ, and cyclopentanones at 5.73–5.74 μ. Confinement of the carbonyl group in a small ring quite commonly results in a shift of the C=O vibration to lower wave lengths. See R. N. Jones, *et al.*, THIS JOURNAL, **70**, 2024 (1948).

(23) D. Vorländer and K. Hobohm, *Ber.*, **29**, 1836 (1896).

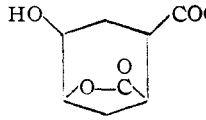
(24) H. S. French and M. E. T. Holden, THIS JOURNAL, **67**, 1240 (1945).

(25) Unless skeletal rearrangement has occurred in the formation of picrotoxinide. This (unlikely) possibility will be excluded by the subsequent evidence.

(26) The alternative meta-bridged five-membered lactones are rendered decidedly improbable by the infrared spectra since such structures would be expected to exhibit carbonyl absorption at a wave length considerably lower than that (5.70 μ) consistently observed in the derivatives and in tetrahydrodesoxypicrotoxinide. Thus the substance

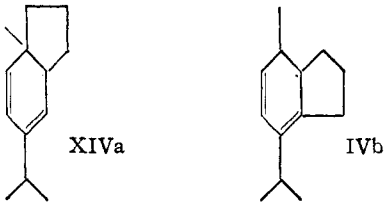


obtained from the adduct of α-pyrone and maleic anhydride, gives a lactone band at 5.69 μ (B. Landau, Ph.D. Thesis, Harvard University, 1950), but the compound



absorbs at 5.60 μ (G. Stork and S. S. Wagle, unpublished observations).

consumed. The desoxy compound (XIIa or XIIb) was converted to its benzoate (XIIIa or XIIIb), which underwent smooth pyrolysis with the formation of carbon dioxide, benzoic acid and a liquid hydrocarbon, designated picrotoxadiene (XIVa or XIVb).



XIVa IVb

Picrotoxadiene is a conjugated, homoannular diene as indicated by its ultraviolet spectrum (λ_{max} 258 mμ, log E 3.6) and by the fact that it gives a crystalline maleic anhydride addition product in good yield under mild conditions. A compound of structure XIVb, having relevant structural features similar to levopimaric acid, might be expected to absorb at the same wave length as that substance, *i.e.*, at 272.5 mμ,[27] so the result for picrotoxadiene favors XIVa, which is less substituted and so would probably absorb near 260 mμ. More convincing evidence was obtained from attempted dehydrogenation experiments. The diene was recovered unchanged after treatment either with selenium or with palladium–charcoal at the reflux temperature of 213°, although a substance of formula XIVb would be expected to aromatize readily under these conditions.

Direct and positive proof of the constitution of picrotoxadiene was finally obtained through total synthesis of that substance and its derivatives, work which will be reported in the second article of this series.

Acknowledgment.—The anthor is indebted to the National Institutes of Health for a Public Health Service Research Fellowship, and to S. B. Penick & Company for a generous gift of picrotoxin.

Experimental[28]

Picrotoxinide.—Dihydro-α-picrotoxininic acid[15] (m.p. 232°, dec.) (14.3 g.) was heated cautiously with a free flame; the substance effervesced briskly on melting. When a clear melt was obtained, the gas evolution nearly ceased, and heating was discontinued. The loss in weight was 2.7 g. (calculated for loss of the theoretical amount of carbon dioxide and water, 2.84 g.). The substance on cooling set to a clear, nearly colorless, glass which stubbornly resisted all attempts to induce crystallization.

Dihydropicrotoxinide.—The glassy picrotoxinide obtained above was dissolved in 100 cc. of methanol, and, after the addition of 0.3 g. of platinum oxide, was hydrogenated at atmospheric pressure. The absorption of hydrogen was very rapid; 95% of the theoretical amount was taken up in ten minutes. The black colloidal suspension was evaporated to dryness *in vacuo*, and the residue taken up in chloroform. After the solution was shaken with saturated aqueous sodium sulfate the platinum coagulated and was removed by filtration. The organic layer was separated and evaporated to dryness; the crystalline residue was purified by recrystallization from methanol–ether. The yield was 10.2 g. (89 % based on dihydro-α-picrotoxininic acid) of colorless needles, m.p. 185.0–186.5°. For analysis a sample was recrystallized from methanol–ether, m.p. 187.2–187.8°.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.82; H, 8.11.

Dihydropicrotoxinide 2,4-dinitrophenylhydrazone was recrystallized from ethanol, and formed golden leaflets, m.p. 209°, dec.

Anal. Calcd. for $C_{20}H_{24}O_7N_4$: C, 55.53; H, 5.60. Found: C, 55.42; H, 5.55.

Dibenzylidene Dihydropicrotoxinide.—One gram of dihydropicrotoxinide was dissolved in excess methanolic potassium hydroxide; five grams of benzaldehyde was added. The solution, which rapidly became deep yellow, was allowed to stand at room temperature for one week. The methanol was removed *in vacuo* and the yellow residue dissolved in water. The aqueous solution was extracted several times with ether to remove the excess benzaldehyde, and was then acidified. The deep yellow oily acid which precipitated was allowed to stand at room temperature for several hours, when it relactonized spontaneously to the crystalline dibenzylidene dihydropicrotoxinide. For analysis a sample was recrystallized from cyclohexane; yellow leaflets, m.p. 127–128°.

Anal. Calcd. for $C_{28}H_{28}O_4$: C, 78.48; H, 6.59. Found: C, 78.43; H, 6.74.

Dihydropicrotoxinide Ethylene Mercaptal.—A solution of 10 g. of dihydropicrotoxinide and 4.5 g. of ethane-1,2-dithiol in 50 cc. of chloroform was saturated with gaseous hydrogen chloride and then allowed to stand at room temperature for five hours. The crystalline residue left on evaporation of the chloroform was recrystallized from methanol; yield 12.4 g. (95%) of material, m.p. 250°. For analysis a sample was recrystallized from methanol; it had m.p. 250.5–250.8°.

Anal. Calcd. for $C_{16}H_{24}O_3S_2$: C, 58.50; H, 7.36. Found: C, 58.52; H, 7.38.

Tetrahydrodesoxypicrotoxinide.—Ten grams of the ethylene mercaptal and Raney nickel[29] from 300 g. of alloy were suspended in 800 cc. of ethanol and the mixture stirred at room temperature overnight. The nickel was removed by filtration and washed thoroughly with methanol. The combined filtrate was evaporated to dryness and the residue crystallized from ethyl acetate–cyclohexane. The yield of material with m.p. 162° was 6.7 g. (92%). For analysis a sample was recrystallized from ethyl acetate–cyclohexane, needles or blades, m.p. 162.2–162.8°.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.65; H, 9.41.

Tetrahydrodesoxypicrotoxinide Benzoate.—A mixture of 6.60 g. of tetrahydrodesoxypicrotoxinide, 4.08 g. of freshly distilled benzoyl chloride and 15 cc. of pyridine was allowed to stand at room temperature for three hours. Excess dilute hydrochloric acid was added and the benzoate was extracted with ether. After a bicarbonate-wash the ether was evaporated and the residue crystallized from cyclohexane–petroleum ether (b.p. 30–60°). The original needles weighed 11.7 g., but apparently contained cyclohexane of crystallization, since in the air they gradually crumbled to a crystalline powder, m.p. 134°, weighing 9.0 g. (95%). For analysis a sample was recrystallized from cyclohexane. The m.p. after removal of solvent of crystallization was 134.5–134.8°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.56; H, 7.88.

Picrotoxadiene.—The benzoate obtained above (8.85 g.) was distilled slowly at atmospheric pressure until a small residue (0.15 g.) remained. The semisolid distillate was dissolved in ethyl acetate and washed three times with sodium bicarbonate solution. The solvent was removed and the fragrant liquid hydrocarbon remaining was fractionated. The yield of material of b.p. 212–214° was 3.1 g. (68%).

Picrotoxadiene–Maleic Anhydride Adduct.—Picrotoxadiene (176 mg.) was heated with 98 mg. of maleic anhydride at 100° for 15 minutes. The anhydride first melted, forming a separate liquid phase, but in the course of several minutes the phases suddenly coalesced into one. On cool-

(27) G. C. Harris and T. F. Sanderson, THIS JOURNAL, 70, 334 (1948); K. Kraft, *Ann.*, 520, 133 (1935).

(28) All melting points are corrected. All ultraviolet absorption spectra were taken in absolute ethanol.

(29) A. A. Pavlic and H. Adkins, THIS JOURNAL, 68, 1471 (1946).

ing, the adduct solidified, and was recrystallized from 30–60° petroleum–ether. The yield of material with the m.p. 75° was 235 mg. (86%). For analysis a sample was recrystallized from petroleum–ether, m.p. 75.0–75.6°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.51; H, 8.31.

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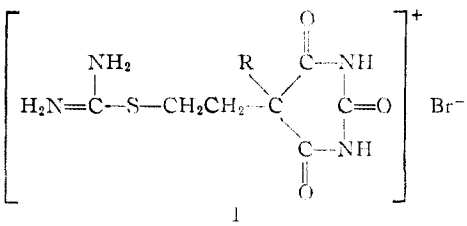
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Thiocyanate and Isothiourea Derivatives of Barbituric Acid

BY GLENN S. SKINNER AND WILLIAM H. WAITZ, JR.

A series of thiocyanate and isothiourea derivatives of barbituric acid have been prepared and subjected to pharmacological testing. The thiocyanate resisted hydrolysis without cleavage of the ring. The isothiourea derivative was smoothly hydrolyzed to the mercaptobarbituric acid. None of the compounds gave hypnosis or anesthesia. The isothiouronium bromides showed some anticonvulsant activity.

In a previous report[1] we have described a series of 5-(β-xanthoethyl)- and 5-(β-mercaptoethyl)-barbituric acids. The establishment of the carbon–sulfur bond at this position has now been extended to include the thiocyanates and isothiouronium salts (I).



I

Both the thiocyanates and the isothiouronium salts (Table I) were easily prepared in good yields by the action of potassium thiocyanate and thiourea, respectively, on the β-bromoethylbarbituric acid derivatives in alcohol. These reagents are advantageous since they are more stable than the xanthates.

TABLE I

BARBITURIC ACIDS RR'C(CONH)$_2$CO

(R_1, $NCSCH_2CH_2$–; R_2, $(H_2N{=}C(NH_2)SCH_2CH_2–)^+Br^-$; R_3, $HN{=}C(NH_2)SCH_2CH_2$–)

No.	R	R'	M.p., °C.	Nitrogen, % Calcd.	Found
I	C_2H_5-	R_1	193–194	17.41	17.32
II	n-C_3H_7-	R_1	203–204	16.46	16.39
III	*n*-C_4H_9-	R_1	198–199	15.60	15.53
IV	*n*-C_5H_{11}-	R_1	202–203	14.82	14.71
V	*i*-C_5H_{11}-	R_1	197–198	11.32[b]	11.41
VI	C_2H_5-	R_2	284–285[a]	23.56[c]	23.52
VII	*n*-C_3H_7-	R_2	288–289[a]	22.62[c]	22.56
VIII	*n*-C_4H_9-	R_2	302–303[a]	21.76[c]	21.70
IX	*n*-C_5H_{11}-	R_2	296–297[a]	20.96[c]	20.93
X	*i*-C_5H_{11}-	R_2	293–295[a]	20.96[c]	21.01
XI	C_2H_5-	R_3	153–155[a]	21.69	21.72
XII	*n*-C_3H_7-	R_3	148–149[a]	20.58	20.38
XIII	*n*-C_4H_9-	R_3	168–170[a]	19.56	19.46
XIV	*n*-C_5H_{11}-	R_3	169–171[a]	18.65	18.53
XV	*i*-C_5H_{11}-	R_3	187–188[a]	18.65	18.50

[a] Decomp. temp. raised 5°/min. [b] Sulfur. [c] Bromine.

The thiocyanobarbituric acid derivatives appear not to be hydrolyzed by hydrochloric acid except under conditions severe enough to rupture the ring. The isothiouronium salts are easily hydrolyzed by ice-cold alkali to the β-mercaptoethylbarbituric acids in excellent yield.

The isothiouronium salts are converted to the isothiourea derivatives by treatment of their warm aqueous solutions with a slight excess of ammonia. These isothiourea derivatives are also stable white crystalline compounds. The mercapto acid can be obtained in excellent yield by the action of cold aqueous alkali on the isothiouronium salt. This route to the mercapto acid is superior to the xanthate procedure.

The thiocyanates, by vein in rats, gave no anesthesia and produced convulsions. The dose at which 50% of them died varied between 24 and 35 milligrams per kilogram. The isothiouronium bromides administered by mouth in cats (50 mg./kg.) gave no anticonvulsant action by the electrical method. Using the metrazol method, by mouth in rats, the relative anticonvulsant activities as compared to phenylacetylurea were as follows: VI, 1.0; VII, 0.5; VIII, none; IX, 0.5; X (cats), none. VI by vein in rats gave no hypnosis or anesthesia with doses of 50 to 600 mg./kg. None of the other bromides gave hypnosis or anesthesia; the LD_{50} values were as follows: VII, 141; VIII, 69; IX, 47; X, 49. These tests were made by Eli Lilly and Company.

Experimental

5-Alkyl-5-(β-thiocyanoethyl)-barbituric Acids.—In a typical preparation 22.4 g. (0.23 mole) of potassium thiocyanate and 52.6 g. (0.20 mole) of 5-ethyl-5-(β-bromoethyl)-barbituric acid were swirled with 125 cc. of absolute alcohol to effect partial solution. The mixture was heated under reflux (bath 95°) to give a dark red solution which slowly became yellow in the course of an hour. A white precipitate gradually separated and after four hours the contents of the flask appeared to be solid. Heating at this temperature was continued for seven hours. The solid mass was disintegrated while still hot so that it could be removed from the flask after cooling in an ice-bath. The filtered precipitate was washed separately on the buchner funnel with alcohol and with cold water until the filtrate no longer gave a test for bromide ion. The filtered alcohol solution was concentrated to yield more of the product, total yield 41.6 g. (86%). For the analysis it was crystallized from alcohol.

5-Isoamyl-5-(β-thiocyanoethyl)-barbituric acid (1.44 g.) dissolved in 4 cc. of glacial acetic containing 0.27 g. of hydrogen chloride when heated to 60°. Water (0.09 cc.) was added and the mixture was heated for five hours at 60°. The crystalline material which separated on cooling was identical with the starting material. The residue from the solvent was also identical. A similar mixture after heating two hours in a sealed tube at 150° likewise gave only the starting material. A mixture of this acid (0.2 g.), 1.0 cc. of hydrochloric acid (1.19) and 3.0 cc. of glacial

(1) G. S. Skinner and J. B. Bicking, THIS JOURNAL, 72, 1140 (1950).