Anal. Calcd. for $C_{16}H_{20}F_3N_3O_7S_2$: C, 39.42; H, 4.14; N, 8.63; propionyl value, 35.17. Found: C, 39.76; H, 4.14; N, 8.27; propionyl value, 33.95.

Pyrolysis of the Mixture of Tripropionyl Derivatives. A.—In the dry state, at 225 or 250°, only black tars were obtained. When 0.5 g. of the *mixture* was placed in a 6-inch test-tube and immersed in an oil-bath preheated to 210–215°, the solid, originally colorless, had become dirty gray in color in about 5 minutes and a black tarry melt was beginning to appear in about 10 minutes. The tube was removed from the oil-bath and the dark colored solid recrystallized from water to give 0.2 g. (46% yield) of 3-ethyl-7-propionylsulfamyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide (XVI), m.p. 282–283° dec.

Anal. Calcd. for $C_{13}H_{14}F_3N_3O_5S_2$: C, 37.77; H, 3.42; N, 10.17; propionyl value, 13.56. Found: C, 37.83; H, 3.37; N, 10.19; propionyl value, 14.06.

B.—The *tripropionyl mixture*, 31 g., was dissolved in 310 ml. of Dowtherm A preheated to 210°, the solution was kept two hours at 210–215°, cooled, and the crystalline solid filtered. The solid was washed with ethyl ether and recrystallized from aqueous isopropyl alcohol (1:1) to give 10 g. (42% yield) of 3-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XV), m.p. 345–347° dec.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_4S_2$: C, 33.61; H, 2.83; N, 11.76; S, 17.94. Found: C, 33.22; H, 2.92; N, 11.57; S, 17.99.

Alternately, 5 g. of the **tripropionyl mixture** was dissolved in 50 ml. of Dowtherm A, preheated to 210°, the solution was kept two hours at 210–215°, cooled, the solid filtered and washed with hexane. The crude solid, 3.5 g., was stirred for one hour at room temperature with 200 ml. of ethyl acetate. The insoluble material weighed 2.0 g. and after recrystallization from water there was obtained 1.8 g. of product, m.p. 345–347° dec.; a mixture m.p. with XV obtained above was 345–347° dec. The infrared absorption curves of the two compounds were identical. The ethyl acetate filtrate concentrated to dryness gave 0.8 g. of residue; this was recrystallized from aqueous isopropyl alcohol to give 0.6 g. of product, m.p. 282–283° dec. A mixture m.p. with XVI obtained above was 282–283° dec. and the infrared absorption spectra of the two compounds were identical.

7-Acetylsulfamyl-3-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide.—A mixture of 1.0 g. of XV and 40 ml. of acetic anhydride were refluxed for 2 hours, cooled, and the solid filtered. A recrystallization from aqueous ethanol gave the product, m.p. 296–297°. This compound again shows absorption at 5.77 μ.

Anal. Calcd. for $C_{12}H_{12}F_3N_3O_5S_2$: C, 36.08; H, 3.03; N, 10.52. Found: C, 35.99; H, 2.93; N, 10.71.

5-Acetamido-α,α,α-trifluoro-2,4-toluenedisulfonamide (XVII).—A mixture of 19.2 g. (0.06 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide, 12.2 g. (0.12 mole) of acetic anhydride and 100 ml. of glacial acetic acid was heated under reflux for 3 hours and then concentrated to dryness. The residual glass was warmed with 50 ml. of water until it solidified. The solid was filtered and air-dried to give 17 g. of material, m.p. 224–226° dec. Recrystallization from aqueous acetonitrile gave 14.5 g. (67% yield) of product, m.p. 234–236°.

Anal. Calcd. for $C_9H_{10}F_3N_3O_5S_2$: C, 29.91; H, 2.79; N, 11.63. Found: C, 30.53; H, 3.30; N, 11.71.

Two and one-half grams of XVII in a six-inch test-tube was placed in an oil-bath preheated to 200° and the temperature allowed to rise to 250° within a 2-hour period. No fusion was apparent, the white solid merely becoming gray in color and somewhat porous. This solid was recrystallized from water to give 1.5 g. (63% yield) of 3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XIII), m.p. 338–340°.

Pyrolysis of 2.5 g. of XVII in 15 ml. of Dowtherm A at 210–215° gave a 47% yield of XIII, m.p. 338–340°.

Diacetyl Derivative of 5-Amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (XVII).—A mixture of 5 g. (0.016 mole) of I and 15 ml. of acetic anhydride was heated on the steam-bath for one hour, cooled, the solid filtered and washed with ether. The yield was 6 g. (95%), m.p. 178–180° dec. An analytical sample recrystallized from aqueous ethanol melted unchanged at 178–180° dec.

Anal. Calcd. for $C_{11}H_{12}F_3N_3O_6S_2$: C, 32.75; H, 3.00; N, 10.42; acetyl, 21.34. Found: C, 33.09; H, 3.40; N, 9.88; acetyl, 21.89.

Pyrolysis of 3 g. of XVII in 15 ml. of Dowtherm A at 210–215° gave a product, m.p. 306–308° after recrystallization from water. The infrared spectrum of this material showed a weak band at 5.85 μ, indicative of the presence of XII, as well as bands at 6.15, 6.23, 6.30 and 6.62 μ. The analytical data obtained on this material (C, 32.06; H, 2.81; acetyl, 3.34) would indicate that about 25–35% of XII was present in the mixture.

3-Oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XXI).—Three and two-tenths grams (0.01 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide and 0.6 g. of urea were ground thoroughly in a mortar and placed in an oil-bath preheated to 200°; the mixture fused and resolidified during 0.5 hour. The crude solid melted at 305–307° dec. A recrystallization from water containing several drops of dilute hydrochloric acid gave the pure product, m.p. 315–317° dec. The yield was 1.5 g. (28% yield). In the infrared, XXI showed a strong band at 5.82 μ and weaker bands at 6.22, 6.33 and 6.55 μ.

Anal. Calcd. for $C_8H_6F_3N_3O_5S_2$: C, 27.83; H, 1.75; N, 12.17. Found: C, 28.15; H, 2.11; N, 12.04.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. IV.[1] 6,6-Dimethyl-11-keto-6,11-dihydrobenz[b]acridans

BY N. H. CROMWELL AND JOHN C. DAVID

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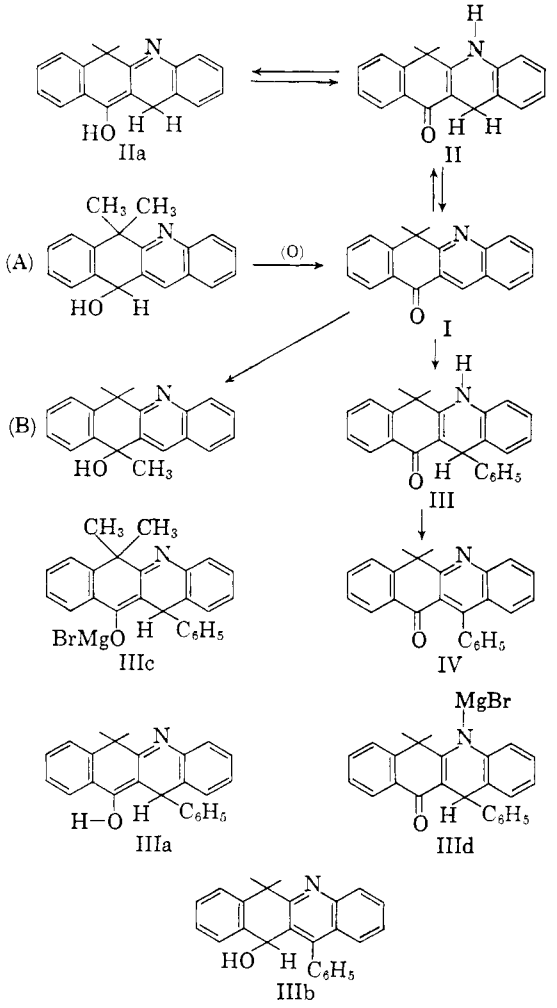
Catalytic hydrogenation and reaction with phenylmagnesium bromide converted 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridine (I) into 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridan (II) and 6,6-dimethyl-11-keto-12-phenyl-6,11-dihydrobenz[b]acridan (III), respectively. Dehydrogenation of II re-formed I while III produced the corresponding 12-phenyl derivative IV. Absorption spectra studies of II and III show them to have the expected characteristics of β-amino-α,β-unsaturated ketones when compared with an authentic member of this class of compounds, 1-phenyl-3-anilino-2-butene-1-one (V).

In a previous investigation[1] the hydrolysis of 6,6-dimethyl-11-bromo-6,11-dihydrobenz[b]acridine produced 6,6-dimethyl-11-hydroxy-6,11-dihydrobenz[b]acridine (A) which oxidized in the air to 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridine (I). With the thought that better yields of A might be obtained by the hydrogenation of the readily available[1] keto compound I various hydrogenation experiments were carried out. No evidence for the formation of A was obtained using

(1) For paper III see, N. H. Cromwell and J. C. David, THIS JOURNAL, **81**, 1138 (1959).

various reagents such as lithium aluminum hydride in ether, or palladium-on-charcoal in ethyl acetate. In benzene solution with three atmospheres of hydrogen, this latter catalyst produced a yellow colored crystalline product whose elementary analysis and absorption spectra studies, as discussed later, indicated it to be mainly 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridan (II). An authentic 11-hydroxy derivative, 6,6,11-trimethyl - 11 - hydroxy - 6,11 - dihydrobenz[b]-acridine (B) had previously[1] been obtained from the reaction of I with methylmagnesium iodide.



Recently Fuson and Miller[2] described the conjugate addition of phenylmagnesium bromide to what may be considered as an open model of I, 3-benzoylquinoline. Mainly on the basis of spectral evidence the 3-benzoyl-4-phenyl-1,4-dihydroquinoline structure was assigned to the product. Reaction of the ketodihydrobenzacridine I with phenylmagnesium bromide under conditions similar to those employed by Fuson and Miller resulted in the high-melting, yellow colored crystalline compound III with physical characteristics similar to those described for the 3-benzoylquinoline addition product, and for the reduction product II. As is discussed in detail later, the spectral studies indicated II and III to have similar structures both being keto dihydrobenz(b)acridans.

In a manner analogous to the chloranil aromatization of 3-benzoyl-4-phenyl-1,4-dihydroquinoline to 3-benzoyl-4-phenyl quinoline,[2] both II and III were readily converted to I and 6,6-dimethyl - 11 - keto - 12 - phenyl - 6,11 - dihydrobenz(b)acridine (IV), respectively.

There seems to be little question that the mode of formation of III is analogous to that of 3-benzoyl-4-phenyl-1,4-dihydroquinoline reported by Fuson and Miller.[2] The apparent assumption of these authors that the carbonyl group is involved in the reaction would require by inference that III is formed by the 1,4-addition of the Grignard reagent forming the complex IIIc which would then hydrolyze to give III, IIIa or IIIb.

Etienne[3] has described the addition of phenylmagnesium bromide to benz(g)quinoline to produce the 2-phenyl derivative. While the failure of the phenyl group to appear in the 2-position of the 3-benzoylquinoline moiety may have been considered by Fuson and Miller[2] to preclude the formation of their product by direct addition of the Grignard reagent to the heterocycle, the possibility of 1,4-addition of the reagent to the heterocyclic ring in I (complex IIId), in which the position adjacent to the nitrogen is blocked, cannot be excluded.[4] No evidence was obtained in these studies for tautomerism between benzacridine and benzacridan forms (*i.e.*, III ⇄ IIIa ⇄ IIIb). Treatment of A with acid or base did not produce II in detectable quantities.

Absorption Spectra and Structure of the Ketodihydrobenz(b)acridans.—The structures of the 6,6-dimethyl-6,11-dihydrobenz(b)acridines in which carbon-11 is saturated, discussed in a previous communication,[1] is most clearly evidenced by the similarity of their ultraviolet spectra to that of quinoline. If hydrogenation and/or reaction of phenylmagnesium bromide with the keto dihydrobenz(b)acridine I had involved a 1,2-addition to the carbonyl group, the ultraviolet spectra of the products would have resembled the spectra of quinoline and of the authentic 6,6-dimethyl-6,11-dihydrobenz(b)acridines, as previously reported.[1] Actually the ultraviolet spectra of II and III showed characteristics which have been established for β-amino-α,β-unsaturated ketones.[5] The keto acridans both showed strong maxima at 246–248 and 372–381 mμ while the open-chain analogs 1-anilino-2-benzoylethylene[5b] and 1-phenyl-3-anilino-2-butene-1-one(V) have similarly shaped absorption curves with maxima at 244 and 372 mμ and 244 and 353 mμ, respectively.

As part of an investigation as to the possibility of II and III existing as their enol tautomers IIa and IIIa under some circumstances, the ultraviolet spectra were measured in 0.1 *N* methanolic hydrogen chloride and sodium methoxide solutions. Similar studies have been reported by Specker and

(2) R. C. Fuson and J. J. Miller, THIS JOURNAL, **79**, 3478 (1957).

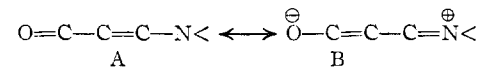
(3) A. Etienne, *Ann. chim.*, **12** [1], 1 (1946).

(4) See, for example, E. Bergmann, O. Blum-Bergmann and A. F. von Christiani, *Ann.*, **483**, 80 (1930), who discuss the 1,4-addition of organometallic compounds to the 5- and 10-positions of acridine.

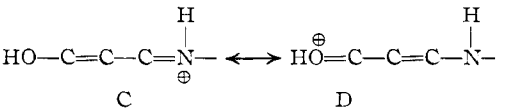
(5) (a) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949); (b) K. Bowden, E. Braude, E. R. H. Jones and B. Weedon, *J. Chem. Soc.*, 948 (1946).

Gawrosch[6a] for 2- and 4-pyridones, Ewing and Steck[6b] for quinolinols, and Mason[6c] for various related N-heteroaromatic hydroxy compounds and their tautomers. It was found that the ultraviolet spectra of II and III were essentially unaffected by base, but that III exhibited a slight, and II a considerable bathochromic shift in 0.1 *N* methanolic hydrogen chloride. On the other hand, the acid spectrum of the open chain analog V showed a sizable hypsochromic shift accompanied by a loss in intensity.

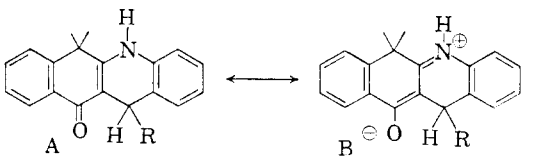
The absorption of ultraviolet light at the longer wave lengths by open-chain β-amino-α,β-unsaturated ketones has been ascribed[5a] to the electronic transition A↔B.



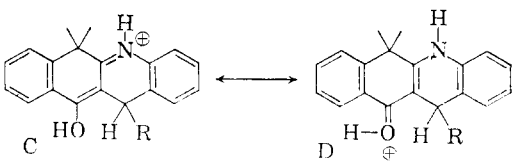
Thus the hypsochromic shift in acid solution exhibited by V is expected because of the unavailability of the electrons on the nitrogen atom of the keto nitronium ion for conjugation. The acid spectra of II and III strongly suggest that the ground states of these compounds in acid solution are in the enol forms IIa and IIIa. The "shift" observed results from an unrelated transition and it may be bathochromic or hypsochromic depending upon the comparative energy requirements of the two unrelated transitions A↔B and C↔D. It is proposed that the bathochromic shifts ob-



served in the acid solutions of the keto acridans II and III are due to a change from the keto form transitions of type A ↔ B, to the enol from transi-



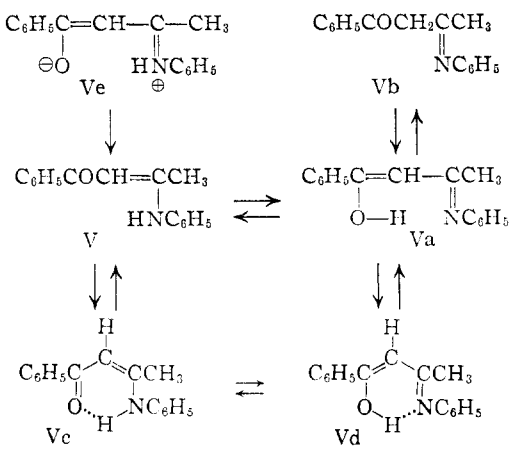
tions, C↔D, in which no separation of charge or loss of aromaticity is involved. Apparently the large steric requirements of the 12-phenyl group



in II cause it to inhibit transition C↔D even more than it inhibits the transition A ↔ B which has similar but not identical steric requirements. The enolization of these cyclic β-amino-α,β-unsaturated ketones, the keto acridans II and III, in acid solution is unique. These constitute the first recognized examples of the enolization of β-amino-α,β-unsaturated-ketones, the enol forms of which are not created through aromatization.[6] Apparently the enol form IIIa is especially well stabilized in acid solution. In the case of the 4-pyridones and 4-quinolones the enolic forms are aromatic.[6]

The infrared spectra of the keto acridans II and III in the solid state in the form of Nujol mulls showed strong free N–H band absorption at 3305 and 3280 cm.$^{-1}$, respectively, while the solid state spectrum of the open-chain analog V gave no absorption in this area. The solid phase spectra of II and III also showed broad bands in the intermolecular hydrogen bonded N–H area[7] between 3200 and 3260 cm.$^{-1}$. The insolubility of II and III in carbon tetrachloride necessitated the use of the associating solvent chloroform for the solution studies. In solution both II and III showed a free N–H band at 3462 cm.$^{-1}$ and intermolecular hydrogen bonded N–H bands at 3342 and 3360 cm.$^{-1}$, respectively. Compound III also showed a weak band in the O–H region at 3630 cm.$^{-1}$ which may be the result of some enolization (III → IIIa) in this medium or due to a contaminant such as the tertiary carbinol from the 1,2-addition of phenyl Grignard to I (Fuson and Miller[2] isolated such products in the 3-aroylpyridine series).

The solution infrared spectrum of V showed a free N–H band at 3455 cm.$^{-1}$ and a weaker but sharp band in the O–H region at 3601 cm.$^{-1}$. This may indicate that in the associating solvent chloroform compound V exists as a tautomeric mixture (V ⇄ Va). In the solid phase and in a non-associating solvent, carbon tetrachloride, this β-amino-α,β-unsaturated ketone would seem to exist as a chelated structure Vc ⇄ Vd, since the N–H and/or O–H bands are very wide (200 cm.$^{-1}$ wide at half-extinction) and shifted into the 2800–3100 cm.$^{-1}$ region of the spectrum where they are blended with the C–H band absorption.



From a study of the infrared spectra of eight open-chain β-amino-α,β-unsaturated ketones in the solid state, Cromwell, *et al.*,[8] concluded that carbonyl absorption is exhibited in these spectra but that the maxima are lowered by 20–80 cm.$^{-1}$ from

(6) (a) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942); (b) C. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 2181 (1946); (c) S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

(7) See J. Weinstein and G. M. Wyman, *J. Org. Chem.*, **23**, 1618 (1958), for an excellent study of the 3000–4000 cm.$^{-1}$ and 1700–1500 cm.$^{-1}$ area of the spectrum for various open chain β-amino-α,β-unsaturated ketones.

(8) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, THIS JOURNAL, **71**, 3337 (1949).

those of the parent α,β-unsaturated ketones and that their spectra resemble those of amides of which they are vinylogs. It was suggested that this large carbonyl shift is due to the combined effect of conjugated chelation (intramolecular hydrogen bonding) and contribution to the ground state by an electronic distribution similar to that of the enol forms. The recent solution and solid phase work of Weinstein and Wyman[7] has confirmed these findings and in addition has given evidence for intermolecular hydrogen bonding with some of these compounds.

As bicyclic β-amino-α,β-unsaturated ketones, the ketodihydrobenz(b)acridans, II and III, represent what appears to be the first members of this class so recognized. Their infrared spectra should reflect contributions by resonance (A) $\leftrightarrow$ (B) and intermolecularly hydrogen bonded forms.

The double bond stretching region of β-amino-α,β-unsaturated ketones is difficult to interpret.[7,8] The presence of two N–H stretching bands in the solution spectra of II and III would indicate the presence of at least two distinct species in this state and would seem to require the assignment of two bands above 1600 cm.$^{-1}$ to C=O stretching. Thus for II the absorption at 1620 cm.$^{-1}$ may be assigned to the non-hydrogen bonded form while the band at 1595 cm.$^{-1}$ is assigned to the C=O stretching frequency of the intermolecularly hydrogen bonded form. The solid state spectrum of II, which also seems to reflect the presence of at least two species, shows four bands of similar intensity at 1620, 1611, 1588 and 1568 cm.$^{-1}$, with the most intense band at 1588. Assignment of bands under these circumstances is not feasible, but certainly the carbonyl stretching frequencies are to be found in this group of bands.

Both the solid and solution spectra of III show only one strong band between 1700 and 1600 cm.$^{-1}$, at 1622 and 1613 cm.$^{-1}$, respectively, which may be assigned to a carbonyl stretching vibration with some confidence. A study of the N-methylated derivatives of II and III would do much to clarify this situation.

The double bond region of the infrared spectrum of V is also difficult to interpret. In carbon tetrachloride, chloroform or as a Nujol mull the spectrum shows four strong bonds between 1617 and 1522 cm.$^{-1}$. Even though it is not the strongest band in the area, we are inclined to assign the higher frequency one in each case (1609 1607 and 1617 cm.$^{-1}$) to the carbonyl-stretching vibration. As was suggested above this material seems to exist as a tautomeric mixture (V) $\rightleftarrows$ (Va) with resonance contribution (V) $\leftrightarrow$ (Ve) in chloroform solution, and as the chelated structure (Vc) $\rightleftarrows$ (Vd) in carbon tetrachloride solution and in the solid state. No evidence was found for a keto anil structure Vb, as suggested by Edwards and Petrow[9] for the condensation products of acetylacetone and various substituted anilines. Keto anils of type Vb would be expected to show normal benzoyl carbonyl bands near 1690 cm.$^{-1}$ while the anils of acetylacetone should have bands similar to that for acetone near 1718 cm.$^{-1}$. Weinstein and Wyman[7] and Cromwell, *et al.*,[8] found no evidence for keto imine structures in their studies in the acetylacetone series.

In his extensive study of the infrared spectra of a considerable number of N-heteroaromatic hydroxy compounds, Mason[10] found that 4-hydroxyquinoline exists mainly in the vinyl amide form in both the solid and solution states (γ_{N-H} 3442 (CCl_4), 3438 ($CHCl_3$), 3226 and 3140 (solid); $\gamma_{C=O}$ 1645 ($CHCl_3$), 1638 (solid)). The structural factors here are related to but not identical with those of ketodihydrobenz(b)acridans, II and III, discussed above.

6,6-Dimethyl-11-keto-12-phenyl-6,11-dihydrobenz(b)acridine(IV) showed a strong carbonyl band at 1667 cm.$^{-1}$ which compares favorably with the band at 1668 cm.$^{-1}$ for the parent keto compound I.

Acknowledgment.—This investigation was supported by grant CY2931 from the National Cancer Institute, National Institutes of Health.

Experimental[11]

6,6-Dimethyl-11-keto-6,11-dihydrobenz(b)acridan (II).—A suspension of 0.40 g. of 10% palladium-on-charcoal in a solution of 1.50 g. (0.0055 mole) of the keto acridine I[1] in 90 ml. of benzene was shaken under 45 lb./in.^{2} of hydrogen for 3 hours. Most of the 0.621 g. of the yellow crystalline product II was obtained by extraction of the catalyst with ethanol; m.p. 255–268°. Several recrystallizations from ethanol and drying at 140° (0.5 mm.) failed to narrow the melting range of this product; λ_{max} (methanol): 246, 296, 381 mμ ($\epsilon \times 10^{-3}$, 15.7, 2.7, 17.8;) λ_{max} (methanol + 0.1 *N* $NaOCH_3$): 246, 297, 381 mμ ($\epsilon \times 10^{-3}$, 15.8, 4.5, 17.6); λ_{max} (methanol + 0.1 *N* HCl): 256, 409 mμ ($\epsilon \times 10^{-3}$, 15.1, 15.8); infrared bands, in $CHCl_3$ sol., 3462/68, 3342/51, 1620/100, 1595/81, 1567/60; in Nujol, 3305/91, (3260–3240)/74, 3200/69, 1620/81, 1611/87, 1588/93, 1568/85. *Anal.* Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.53; H, 6.11; N, 5.05.

Reaction of II with Chloronil.—A solution of 0.150 g. (0.00054 mole) of II and 0.137 g. (0.00055 mole) of chloranil in 100 ml. of benzene was concentrated to 30 ml. and refluxed for 25 hours. After successive washings with 10% sodium hydroxide and water 43 mg. (30% yield) of pure I, m.p. 135–137°, was obtained from the reaction mixture.

6,6-Dimethyl-11-keto-12-phenyl-6,11-dihydrobenz(b)acridan (III).—A 1.0-g. (0.00356 mole) portion of I was extracted from the thimble of a Soxhlet apparatus into a 12-ml. ether solution of phenylmagnesium bromide formed from 1.235 g. (0.0078 mole) of bromobenzene. The complex was decomposed with a saturated ammonium chloride solution and the product isolated as yellow needles, wt. 1.102 g. (81% yield), m.p. 274–276°, recrystallized from benzene; λ_{max} (methanol): 248, 296, 372 mμ ($\epsilon \times 10^{-3}$, 14.8, 3.2, 16.8); λ_{max} (methanol + 0.1 *N* $NaOCH_3$): 248, 295, 372 mμ ($\epsilon \times 10^{-3}$, 15.0, 3.5, 16.2); λ_{max} (methanol + 0.1 *N* HCl): 252, 296, 376 mμ ($\epsilon \times 10^{-3}$, 14.1, 2.9, 14.5); infrared bands, in $CHCl_3$ sol., 3630/23, 3462/51, 3360/25, 1622/100, 1595/91, 1567/76; in Nujol, 3280/49, 3240-3220/45, 1613/57, 1594/54, 1568/51.

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.31; H, 6.18, N, 3.91.

6,6-Dimethyl-11-keto-12-phenyl-6,11-dihydrobenz(b)acridine (IV).—A solution of 0.20 g. (0.0017 mole) of III and 0.14 g. (0.0018 mole) of chloranil in 100 ml of benzene was refluxed for 20 hours. The reaction mixture was washed with 10% sodium hydroxide and the crude product isolated as an oil. Crystallization from ethanol returned 0.80 g. (40%) of the starting material III and produced 0.056 g.

(9) W. G. H. Edwards and V. Petrow, *J. Chem. Soc.*, 2853 (1954).

(10) S. F. Mason, *ibid.*, 4874 (1957).

(11) Ultraviolet spectra were measured with a Cary instrument model 11 MS using matched 1-cm. fused silica cells. All solutions were studied within five minutes of making them. The infrared spectra were measured with a Perkin–Elmer model 21 instrument employing NaCl optics and matched 1.0-mm. cells for solution studies and recorded as cm.$^{-1}$/% abs.

(28% yield) of IV as yellow colored cubes, m.p. 185–186°, recrystd. from acetone; infrared bands (CCl_4), 1667/92, 1602/12, 1550/24. *Anal.* Calcd. for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.93; H, 5.50; N, 3.89.

1-Phenyl-3-anilino-2-butene-1-one (V).—A sample of this β-anilino-α,β-unsaturated ketone was prepared by the method suggested by Beyer[12] in 43% yield, m.p. 108–110°; λ_{max} (methanol); 244, 353 mμ (ε × 10^{-3}, 13.4, 26.2); λ_{max} (methanol + 0.1 *N* $NaOCH_3$): 244, 353 mμ (ε × 10^{-3}, 13.4, 26.4); λ_{max} (methanol + 0.1 *N* HCl): 244, 307 mμ (ε × 10^{-3}, 7.5, 13.1); infrared bands in $CHCl_3$, 3601/27, 3455/29, 1607/69, 1595/84, 1567/90, 1550/64; in CCl_4, 3060/70, 1609/33, 1596/82, 1570/86, 1559/61; in Nujol, 2930/80, 1617/63, 1589/65, 1549/67, 1522/72.

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Model Reactions for the Biosynthesis of Thyroxine. II. The Fate of the Aliphatic Side Chain in the Conversion of 3,5-Diiodophloretic Acid to 3,5,3′,5′-Tetraiodothyropropionic Acid[1]

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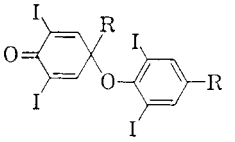
A model reaction for the biosynthesis of thyroxine, the non-enzymic conversion of diiodophloretic acid (diiododesaminotyrosine) to tetraiodothyropropionic acid, has been investigated. The fate of the aliphatic side chain which is eliminated in the course of this reaction has been determined. Hydracrylic acid and dihydracrylic acid are the principal products derived from this side chain. The mechanism of the elimination reaction is discussed.

Introduction

In the biosynthesis of each molecule of thyroxine from two molecules of its precursor 3,5-diiodotyrosine the alanine side chain of one of the two molecules of diiodotyrosine is split off. The fate of this "lost side chain" has been a matter of controversy for many years.

Since the discovery of a simple model reaction for the biosynthesis of thyroxine, the formation of thyroxine in the non-enzymic alkaline incubation of 3,5-diiodotyrosine[3] at 37°, the fate of the alanine side chain in this reaction has been studied by several investigators. Johnson and Tewkesbury[4] postulated that in the conversion of diiodotyrosine to thyroxine a quinol ether intermediate (I) is formed



I, R = $CH_2CH(NH_2)COOH$

which then loses an alanine side chain. They pointed out that this side chain could be lost either as serine or as dehydroalanine (iminopyruvic acid). The latter would hydrolyze to form pyruvic acid and ammonia. According to Harrington[5] serine could be formed not only by the attack of a hydroxyl ion on the quinol ether but also by hydration of the originally formed dehydroalanine.

Johnson and Tewkesbury detected pyruvic acid and ammonia in the incubation mixture but were unable to detect serine. On the other hand, Ohno[6] found serine in the reaction mixture. No experimental data in support of his finding have been reported. Pitt-Rivers[7] who modified von Mutzenbecher's model reaction by substituting N-acetyl-3,5-diiodotyrosine for 3,5-diiodotyrosine and incubating it at *p*H 7.6 found after hydrolysis of the reaction mixture alanine but no serine. Pitt-Rivers pointed out, however, that acetylalanine could have been formed from pyruvic acid and ammonia. In a recent publication Pitt-Rivers and James[8] expressed the opinion that the side chain in this model reaction is split off as hydroxypyruvic acid and acetamide. They were unable to detect hydroxypyruvic acid in the reaction mixture but pointed out that this might be due to the instability of hydroxypyruvic acid.[9] When they incubated a peptide, N-acetyldiiodotyrosyl-ε-N-(α-N-acetyl)-lysine, they could prove the presence of ε-N-hydroxypyruvoyl-α-N-acetyllysine and of acetamide in the reaction mixture. An entirely different model reaction for the biosynthesis of thyroxine was devised by Sela and Sarid.[10] They incubated iodinated polytyrosine and found serine after hydrolysis of the reaction mixture. The incubation was, however, carried out at *p*H 10.2. In this Laboratory an investigation was made with the aim of finding a simpler model reaction for the biosynthesis of thyroxine. Such a reaction was found in the non-enzymic incubation of 3,5-diiodophloretic acid (3,5-diiododesaminotyrosine). This reaction yields 3,5,3′,5′-tetraiodothyropropionic acid (desaminothyroxine) in a yield that is considerably higher than the yield of thyroxine or N-acetylthyroxine obtained in the incubation of diiodotyrosine or N-acetyldiiodotyrosine, respectively.[1] This model reaction was then used to elucidate the fate of the "lost side chain." The reaction mechanism in this case must be assumed to be closely related to the one by which thyroxine is synthesized in von Mutzenbecher's experiment. A knowledge of this

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