Triazines. XXIV. The Conversion of Methyl-*s*-triazines into *s*-Triazine Aldoximes[1]

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Several *s*-triazine mono- and bisaldoximes were obtained readily and in fair yields by the base-catalyzed condensation of the corresponding methyl-*s*-triazines with alkyl nitrites. Hydrolysis of the oximes to the *s*-triazine aldehydes was only possible with 4,6-diaryl-*s*-triazine aldoximes. These aldehydes also could be prepared directly from the 2-methyl-4,6-diaryl-*s*-triazines by reaction with nitrous acid in concentrated sulfuric acid.

During the course of our investigation of novel nitrile oxides,[2] we became interested in the preparation of mono- and difunctional *s*-triazine aldoximes as intermediates. Since the only known route to *s*-triazine aldehydes is limited to monoaldehydes with a narrow choice of possible substituents in the 4- and 6-position,[3] we tried to convert the readily accessible methyl-*s*-triazines (I) into the corresponding aldehydes or aldoximes.

Attempted oxidation of the methyl to the formyl group in 2-methyl-4,6-diphenyl-*s*-triazine (Id) by means of selenium dioxide, chromium trioxide, or chromyl chloride failed, as well as the ozonization of the 2,4,6-tristyryl-s-triazine (II).[4] In all experiments excessive cleavage of the *s*-triazine ring occurred prior to or simultaneously with the oxidation of the methyl group. The Ortoleva–King reaction which has been useful in analogous cases[5] proceeded with trimethyl-*s*-triazine only to the bisquaternary perchlorate (III). III resisted all efforts to convert it into the corresponding bisnitrone.

Ostrogovich, *et al.*,[6] transformed 2-methyl-4,6-dihydroxy-*s*-triazine (Ig) into the 4,6-dihydroxy-*s*-triazine-2-formaldoxime (VIIh) by reaction with dinitrogen trioxide in water; similarly they obtained from 2-benzyl-4,6-dihydroxy-*s*-triazine with nitrosyl chloride (generated *in situ* from ethyl nitrite and hydrochloric acid in acetic acid) the 4,6-dihydroxy-*s*-triazinyl-2-phenyl ketoxime (IX). We have convinced ourselves that these methods are not applicable to any of the triazines (Ia to If) used in this study.

We found then that *s*-triazines having at least one methyl group in the 2-position can be transformed readily and with fair to good yields into the corresponding *s*-triazine aldoximes (VII) by condensation with an alkyl nitrite in the presence of an alkali metal alkoxide. If the starting material contains methyl groups in the 2- and 4-positions, *s*-triazine 2,4-bisaldoximes are formed as the main product. Under milder conditions, however, substantial amounts of the monoaldoxime can be obtained usually. Trimethyl-*s*-triazine (Ia) yields, even under the strongest possible conditions, only the 6-methyl-*s*-triazine 2,4-bisaldoxime (VIIb). We have been unable to convert VIIb further into the *s*-triazine trisaldoxime (VIIc).[7]

A possible reaction mechanism involves as the first step the abstraction of a proton from I to yield the carbanion(IV), a step which is facilitated by the electron withdrawing potential of the *s*-triazine ring. The carbanion(IV) then adds the alkyl nitrite to give the intermediate(V) which stabilizes itself with the loss of alcohol to afford the oximate anion(VI), from which the aldoxime(VII) is generated by reaction with a strong acid. This process can be repeated on a second methyl group, if available, but by then the bisoximate anion will be able to saturate the electron deficiency of the *s*-triazine ring to a point where further proton abstraction from a third methyl group becomes increasingly difficult, explaining the lack of reactivity of the last methyl group in trimethyl-*s*-triazine.[8]

Our experimental results are compiled in Table I.

As bases for the condensation, sodium amide, sodium hydride (in dimethyl sulfoxide), and sodium and potassium alkoxides worked satisfactorily. To obtain preferentially monoaldoximes from dimethyl-*s*-triazines, sodium methoxide (freshly prepared[9]) in ethereal solution is recommended, while potassium *t*-butoxide in ether gave the best yields of bisaldoximes. As predictable from the discussed reaction mechanism, the aliphatic triazines (Ia and Ib) reacted most easily, while the methyldiphenyltriazine (Id) was the least reactive. Id did not condense at all with sodium methylate, and even with potassium *t*-butoxide a considerable amount of starting material always was recovered.

All the oximes obtained are fairly acidic, dissolving easily in cold dilute aqueous sodium carbonate. They are colorless to light yellow solids, difficult to obtain in a well crystallized form, melting usually with decomposition over a rather wide range, even when analytically pure. For this reason we tried to characterize them by their ultraviolet spectrum. All oximes have a well defined maximum in the 247- to 267-mμ region, depending on the other substituents. Since in the dioximes (VIIb and VIIf) the two oximino groups are not conjugated to each other through the *s*-triazine ring, their molar extinction coefficient (ε) is about twice as high as in the corresponding monoximes (VIIa and VIIe). This effect can serve for the approximate spectrophotometrical determination of both species in the

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(1) Preceding communication: A. Kreutzberger and C. Grundmann, *J. Org. Chem.*, **26**, 1121 (1961).

(2) C. Grundmann, *Angew. Chem.*, **75**, 450 (1963).

(3) (a) C. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **79**, 944 (1957); (b) E. Kober and C. Grundmann, *ibid.*, **80**, 5547 (1958).

(4) C. Grundmann and G. Weisse, *Chem. Ber.*, **84**, 684 (1951).

(5) W. Reid and H. Bender, *ibid.*, **89**, 1893 (1956); W. Reid and M. Gross, *ibid.*, **90**, 2646 (1957); F. Kröhnke, *Angew. Chem.*, **75**, 181, 317 (1963).

(6) A. Ostrogovich and V. Crasu, *Gazz. chim. ital.*, **64**, 800 (1934); **66**, 653 (1936); A. Ostrogovich and I. Tanislav, *ibid.*, **66**, 662 (1936).

(7) For other unsuccessful attempts to prepare derivatives of *s*-triazine trialdehyde, *cf.* C. Grundmann and M. B. Fulton, *Chem. Ber.*, in press.

(8) For the same reasons, the base-catalyzed condensation of Ia with benzaldehyde leads, contrary to earlier reports,[4] initially only to the 2-(α-hydroxyphenethyl)-4,6-distyryl-*s*-triazine, m.p., 186–188° (*Anal.* Calcd. for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.72; N, 10.36. Found: C, 80.38; H, 5.77; N, 10.32.), which is dehydrated to II by acids. Grundmann and Weisse recrystallized the crude condensation product from acetic acid and overlooked thereby the formation of the above intermediate.

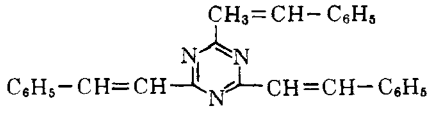
(9) The commercially available product gave generally unsatisfactory results.

TABLE I

CONVERSION OF METHYL-*s*-TRIAZINES INTO *s*-TRIAZINE ALDOXIMES

Starting material (I)			R-ONO	Reaction product (VII)				
R_1	R_2	Base	R	R_1	R_2	Yield, % of theory	M.p., °C.	$\lambda_{\max}^{\mathrm{MeOH}}$, mμ (ε)
CH_3	CH_3	CH_3ONa	C_2H_5	CH_3	CH_3	30[a]	190–209	247 (15,000)[b]
CH_3	CH_3	C_2H_5OK	*i*-C_5H_{11}	CH_3	$CH{=}NOH$	45	*c*	251 (31,400–32,200)[d]
CH_3	CH_3	*t*-C_4H_9OK	*i*-C_5H_{11}	CH_3	$CH{=}NOH$	65	*c*	252.5[e] (38,000)
CH_3O	CH_3O	*t*-C_4H_9OK	*i*-C_5H_{11}	CH_3O	CH_3O	25	215–225	245 (13,800–14,500)[f]
C_6H_5	CH_3	CH_3ONa	C_2H_5	C_6H_5	CH_3	59[g]	183–192	257 (24,500–26,900)[h]
C_6H_5	CH_3	*t*-C_4H_9OK	*i*-C_5H_{11}	C_6H_5	$CH{=}NOH$	54	220–230	262 (41,300–43,300)[i]
C_6H_5	C_6H_5	*t*-C_4H_9OK	*i*-C_5H_{11}	C_6H_5	C_6H_5	79[j]	239–242	267 (50,300–51,900)[k]
C_6H_5	C_6H_5	CH_3ONa	C_2H_5	C_6H_5	C_6H_5	0		

[a] Besides 34% VIIb. [b] Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.01; H, 5.25; N, 37.12. [c] Decomposes gradually between 200 and 300° without melting. [d] Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.60; H, 3.81; N, 38.60. [e] In ethanol. [f] Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.43. Found: C, 39.02; H, 4.37; N, 30.13. [g] Based on 51% recovered starting material, besides 8% VII. [h] Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.44; H, 4.82; N, 25.93. [i] Calcd. for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.80. Found: C, 54.48; H, 3.74; N, 28.63. [j] Based on 64% recovered starting material. [k] Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28; mol. wt., 276. Found: C, 69.55; H, 4.44; N, 20.15; mol. wt. 259.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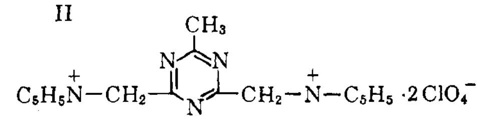
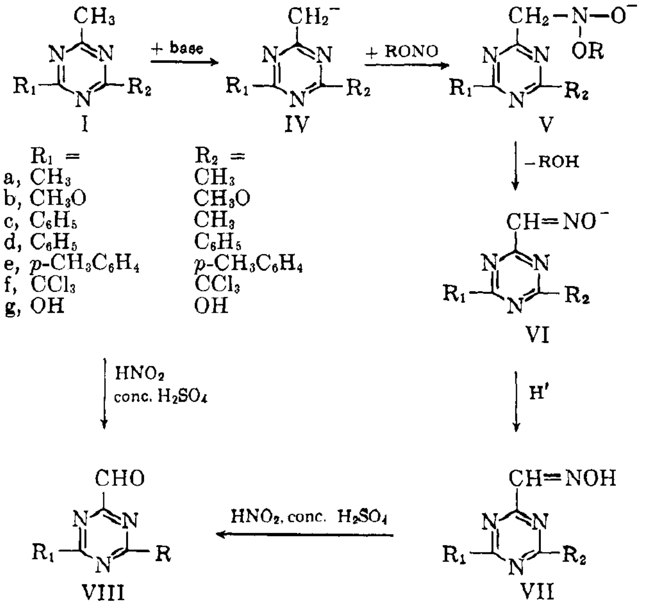
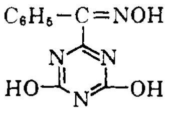

III



$R_1 =$	$R_2 =$
a, CH_3	CH_3
b, CH_3O	CH_3O
c, C_6H_5	CH_3
d, C_6H_5	C_6H_5
e, *p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
f, CCl_3	CCl_3
g, OH	OH

a, $R = C_6H_5$
b, $R = p\text{-}CH_3C_6H_4$

$R_1 =$	$R_2 =$
a, CH_3	CH_3
b, CH_3	$CH{=}NOH$
c, $CH{=}NOH$	$CH{=}NOH$
d, CH_3O	CH_3O
e, C_6H_5	CH_3
f, C_6H_5	$CH{=}NOH$
g, C_6H_5	C_6H_5
h, OH	OH


IX

mixture obtained usually as the raw product of the condensation. However, except for VIIa, analytically pure samples of all oximes showed, in repeated experiments, a variation in ε far beyond the instrumental errors. This indicates that the isolated individual oximes still might be mixtures of *syn* and *anti* forms which we were unable to separate either by recrystallization or by chromatography. The known acetylation technique for distinguishing between *syn*- and *anti*-aldoximes[10] was applied to 2-methyl-6-phenyl-*s*-triazine-2-aldoxime (VIIe) and 4,6-diphenyl-*s*-triazine-2-aldoxime (VIIg). In both cases the corresponding O-acetyloximes were obtained in excellent yields with no trace of nitrile formation detectable by infrared spectroscopy. Alkaline hydrolysis of the recrystallized acetyl derivatives recovered the starting materials apparently unchanged in their physical properties, indicating that both VIIe and VIIg are sterically uniform *syn*-oximes. Thus, if the observed variations in ε are to be explained as discussed above, we must assume that in solution a labile equilibrium between the *anti* and the *syn* form is attained, but that in the acetylation reaction this equilibrium (which may still exist in the solid) shifts quickly to the *syn* isomer, thus simulating steric uniformity.

The bisaldoximes VIIb and VIIf give characteristic intense color reactions with some heavy metal ions: Fe^{+3}, deep purple (very sensitive); Co^{+2}, orange-red; Cu^{+}, deep red-brown. The monoximes VIIa, VIId, and VIIIe give a blue-violet color with Fe^{+2}, but no reaction with ferric ion.

Hydrolysis of the obtained *s*-triazine aldoximes to the corresponding aldehydes proved to be difficult; the oximes were unaffected by alkali, whereas acid hydrolysis using the various modifications recommended in the literature for sensitive carbonyl compounds[11] yielded either unchanged starting material or resulted in complete cleavage of the *s*-triazine ring. Only in the case of the 4,6-diphenyl-*s*-triazine 2-aldoxime (VIIg), which is the most stable of the oximes prepared so far, did reaction with a large excess of nitrous acid in concentrated sulfuric acid at 30° provide the desired aldehyde, 2-formyl-4,6-diphenyl-*s*-triazine (VIIIa), in excellent yield.[12]

We found then that this reagent converted neatly 2-

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(10) A. Hantzsch, *Ber.*, **24**, 13 (1891); O. L. Brady and G. P. McHugh, *J. Chem. Soc.*, **125**, 547 (1924).

(11) Pyruvic and acetic acid [S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. B. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948)], concentrated hydrochloric acid and formaldehyde [P. Fresn, *Ann. chim.* (Paris), [11]**11**, 476 (1939)], dilute hydrochloric acid in acetone [W. T. Sumerford and W. H. Hartung, *J. Am. Pharm. Assoc.*, **29**, 65 (1940)], and excess ethyl-nitrite in dioxane [C. Mannich and H. Budde, *Arch. Pharm.*, **270**, 283 (1932)] were recommended.

(12) This method has been used previously by H. Wieland [*Ann.*, **444**, 31 (1925)] for the preparation of the furoxane dialdehyde from the corresponding dioxime.

methyl-4,6-diphenyl-*s*-triazine (Id) directly into the aldehyde (VIIIa). The reaction goes very likely *via* the oxime (VIIg), but even under very mild conditions we were not able to stop it at that intermediate stage. This convenient reaction seems, however, applicable only to 2-methyl-4,6-diaryl-*s*-triazines.[13] Thus, we have further prepared 2-formyl-4,6-*p*-tolyl-*s*-triazine (VIIIb) from 2-methyl-4,6-di-*p*-tolyl-*s*-triazine (Ie). Sufficient stability against concentrated sulfuric acid seems not to be the only requirement, since the stable 2-methyl-4,6-bistrichloromethyl-*s*-triazine (If) failed to react even under drastic conditions.

Like the known *s*-triazine aldehydes,[3b] VIIIa and VIIIb have a marked tendency to form a hydrate, but these hydrates lose their water easily *in vacuo* over concentrated sulfuric acid, and the products then display a normal carbonyl absorption in the infrared around 1730 cm.$^{-1}$.

Experimental[14]

Starting Materials.—2,4,6-Trimethyl-*s*-triazine (Ia) and 2,4-dimethyl-6-phenyl-*s*-triazine (Ic) were obtained by the excellent procedure of Schaefer.[15] 2-Methyl-4,6-diphenyl-*s*-triazine (Id) and 2-methyl-2,4-*p*-tolyl-*s*-triazine (Ia) were prepared by Pinner's method[16] which gave much better yields and an initially purer product than Kraft's synthesis.[17] 2-Methyl-4,6-dimethoxy-*s*-triazine (Ib) was first described by Russian workers,[18] but their method (heating of 2-methyl-4,6-chloro-*s*-triazine with 10% methanolic potassium hydroxide) gave a product contaminated with hydroxy-*s*-triazines. The following modification yielded a pure material in improved yields.

2-Methyl-4,6-dimethoxy-*s*-triazine (Ib).—2-Methyl-4,6-dichloro-*s*-triazine[19] (4.9 g.) in 60 ml. of anhydrous ether was added dropwise to a stirred, ice-cooled solution of sodium (1.4 g.) in 15 ml. of methanol. The reaction mixture then was refluxed for 30 min. and cooled, and the NaCl formed was filtered and washed with anhydrous ether. The combined filtrates were freed from solvent on the steam bath under reduced pressure, and the residue was dissolved in ether and filtered from insolubles, if necessary. After elimination of the solvent from the filtrate, there remained 4.3 g. (92%) of colorless crystals of Ib, which melted at 67–69° after one recrystallization from petroleum ether (b.p. 30–50°).

Conversion of Methyl-*s*-triazines into *s*-Triazine Aldoximes.—The following typical experiments exemplify the technique used.

6-Methyl-*s*-triazine 2,4-Bisaldoxime (VIIb) and 4,6-Dimethyl-*s*-triazine 2-Aldoxime (VIIa).—To an ice-cooled and stirred solution of sodium (2.0 g.) in methanol (30 ml.) there was added with exclusion of moisture a solution of trimethyl-*s*-triazine (2.58 g.) in 25 ml. of anhydrous ether, followed by an excess of ethyl nitrite (8.5 ml.) in three equal portions. A small yellowish precipitation followed each addition, but soon disappeared. Stirring at 0° was continued for 2 hr. and the reaction mixture then was left overnight at room temperature. To complete precipitation of the orange-red disodium salt of VIIb, 50 ml. of anhydrous ether then was added; the precipitate was filtered, washed thoroughly with ether, and dissolved in 50 ml. of cold water. Upon acidification with 2 *N* sulfuric acid a brownish precipitate of VIIb (0.82 g.) was formed. Exhaustive extraction of the mother liquor with ether in a continuous extractor yielded 0.22 g. more of crude VIIb. Since VIIb is only slightly soluble in all common organic solvents, purification is best achieved by recrystallization from a small amount of water or by dissolving in 2 *N* NaOH, treatment with charcoal, and reprecipitation with mineral acid, yielding VIIb as a tan microcrystalline powder.

The etheral filtrate from the disodium salt of VIIb was freed from solvent under reduced pressure; the remaining red oil (from which no starting material could be isolated) was dissolved in a little water, acidified with 2 *N* H_2SO_4, and extracted with ether in a continuous extractor for 24 hr. On evaporation, the ether extract yielded 0.91 g. of crude monoxime VIIa, which was purified by recrystallization from aqueous acetone to give finally a pale yellow microcrystalline powder, soluble in water, methanol, and tetrahydrofuran.

4,6-Diphenyl-*s*-triazine 2-Aldoxime (VIIg).—A solution of potassium (0.4 g.) in freshly distilled, anhydrous *t*-butyl alcohol (10 ml.) was mixed with a solution of 2-methyl-4,6-diphenyl-*s*-triazine (2.50 g.) in 30 ml. of anhydrous ether, and isoamyl nitrite (1.6 ml.) was added dropwise with ice cooling, stirring, and exclusion of moisture. After 15 min. a pale yellow precipitate appeared. The reaction mixture was refluxed for 30 min. and then left for 2 hr. at room temperature. The precipitated potassium salt of VIIg was filtered and washed with anhydrous ether. From the ethereal filtrate 1.6 g. of starting material could be recovered. The potassium salt of VIIg was hydrolized almost completely to the free oxime when digested for 30 min. with 40 ml. of water on the steam bath. Thus 0.75 g. of VIIg were obtained as a pale yellow crystalline solid. Acidification of the mother liquor yielded 0.04 g. more. The oxime could be recrystallized from aqueous acetone yielding colorless needles; it is insoluble in water and fairly soluble in acetone, benzene, and ethanol.

2-Acetylformoximino-4,6-diphenyl-*s*-triazine.—When 0.69 g. of VIIg was heated with 20 ml. of acetic anhydride to 55–60° for 15 min., 0.718 g. (89%) of the above O-acetyl derivative separated on cooling in well-formed, colorless needles, m.p. 155–165° dec., after two crystallizations from ethanol.

Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.22; H, 4.54; N, 17.47.

By hydrolysis with 2 *N* NaOH the oxime (VIIg, m.p. 242–245° dec.) was recovered in 94% yield.

Analogously, from 4-methyl-6-phenyl-*s*-triazine 2-aldoxime (VIIe) there was obtained the **2-acetyl-formoximino-4-methyl-6-phenyl-*s*-triazine** in colorless leaflets (83%), melting at 116–126° dec. after recrystallization from ethanol. Subsequent hydrolysis with 2 *N* sodium carbonate (45 min. at room temperature) yielded 76% of VIIe, unchanged in its physical and chemical properties.

4,6-Diphenyl-*s*-triazine-2-Aldehyde (VIIIa). A. From 4,6-Diphenyl-*s*-triazine 2-Aldoxime (VIIg).—To a suspension of 0.5 g. of VIIg in concentrated sulfuric acid (5 ml.) there was added finely powdered sodium nitrite (2.4 g.) in small portions keeping the temperature around 30°. After 3 hr. more at room temperature, the reaction mixture was poured on 100 g. of crushed ice, and the precipitated aldehyde immediately was filtered and washed thoroughly with water. The crude product (yield was close to theoretical) melted at 60–70°; it then solidified and melted again at 135–145 with dec. The crude product showed no CO band in the infrared and apparently was an aldehyde hydrate. After drying over concentrated sulfuric acid *in vacuo* for several days at room temperature, however, a sharp carbonyl band at 1720 cm.$^{-1}$ appeared together with a weaker absorption at 2810 cm.$^{-1}$ (C–H stretching), $\lambda_{\max}^{\text{MeOH}}$ 267 mμ ($\epsilon_{\max}$ 34,500). It was easily soluble in methanol, ethanol, and acetone.

For analysis the aldehyde was recrystallized several times from aqueous acetone to yield small needles, m.p. 148–158° dec.

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.35; H, 4.34; N, 15.96.

The **2,4-dinitrophenylhydrazone of VIIIa** crystallized from aqueous ethanol and ethyl acetate in golden, glistening, small needles, m.p. 200–220° dec.

Anal. Calcd. for $C_{22}H_{15}N_7O_4$: C, 59.86; H, 3.43; N, 22.21. Found: C, 59.74; H, 3.61; N, 22.05.

B. From 2-Methyl-4,6-diphenyl-*s*-triazine (Id).—Finely ground sodium nitrite (3.5 g.) was added in small portions over 30 min. to a solution of 1.24 g. of Id in 10 ml. of concentrated H_2SO_4, keeping the temperature as close to 30° as possible. After 2 hr. more at the same temperature, the reaction mixture was diluted with 100 g. of crushed ice, and the almost colorless precipitate was filtered. After one recrystallization from aqueous

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(13) Unsuccessful attempts have been made to apply this method of oxidation to other methyl-substituted heterocyclics, as 4-picoline, 4-picoline-N-oxide, and 4,6-dimethylpyrimidine. Likewise, *o*- and *p*-nitrotoluene and 2,4-dinitrotoluene failed to react.

(14) All melting points were determined with the Fisher-Johns melting point apparatus; microanalyses were performed Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961); F. C. Schaefer, *ibid.*, **27**, 3608 (1962).

(16) A. Pinner and F. Klein, *Ber.*, **11**, 4 (1878); **25**, 1624 (1892); G. Glock, *ibid.*, **21**, 2650 (1888).

(17) F. Kraft and A. von Hansen, *ibid.*, **22**, 803 (1889); F. Kraft, *ibid.*, **23**, 2387 (1890).

(18) N. V. Khromov-Borisov and E. V. Kisareva, *Zh. Obshch. Khim.*, **29**, 3010 (1959); *Chem. Abstr.*, **54**, 12,153*i* (1960).

(19) R. Hirt, H. Nidecker, and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950).

methanol, 1.21 g. (93%) of the aldehyde (VIIIa) was obtained as slightly tan needles, m.p. 145–157° dec.

Slight variations in the above procedures affect the yield considerably; it is especially important that at least a tenfold excess of sodium nitrite is used in A as well as in B.

By the same method as above 69% of **4,6-di-*p*-tolyl-*s*-triazine-2-aldehyde** (VIIIb), from 2-methyl-4,6-di-*p*-tolyl-*s*-triazine (Ie), was obtained as small colorless needles from carbon tetrachloride, m.p. 195–197° dec. The vacuum-dried aldehyde had sharp infrared bands at 1735 and 2820 cm.$^{-1}$, $\lambda_{\max}^{\mathrm{MeOH}}$ 283 mμ ($\epsilon_{\max}$ 47,500), and was easily soluble in acetone, benzene, chloroform, and carbon tetrachloride.

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.32; H, 5.21; N, 14.68.

2,4-Dinitrophenylhydrazine of VIIIb was obtained as small, orange, felted needles (from pyridine), m.p. 269–273° dec.

Anal. Calcd. for $C_{24}H_{19}N_7O_4$: C, 61.40; H, 4.08; N, 20.89. Found: C, 61.35; H, 4.18; N, 20.71.

The Synthesis and Exhaustive Methylation of 5,6,7,8,9,10,6a,10a-Octahydrophenanthridines and Related Compounds[1]

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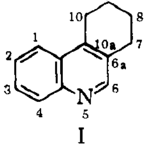
Several methods for preparation of *trans*- and *cis*-5,6,7,8,9,10,6a,10a-octahydrophenanthridines (II) and (V) are described. The confirmation of the configuration of these compounds by stereospecific synthesis and the conformation of the *cis* isomer are discussed. The exhaustive methylation of the stereoisomeric octahydrophenanthridines and octahydroacridines resulted in elimination of methanol.

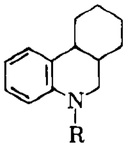
Several years ago we reported the synthesis of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine.[2] The configuration was presumed to be a *trans* modification but was not confirmed. We wish to report the stereospecific synthesis of stereoisomeric octahydrophenanthridines and the exhaustive methylation of these and related compounds.

It appeared that the most logical synthetic route to such bases would involve formation of stereoisomeric amino acids or related compounds which would be cyclized to the phenanthridine nucleus. At first, in view of the stereospecific condensation[3] of *trans*-2-phenylcyclohexanol to *cis*-octahydrophenanthrene, stereoisomers of 2-anilinomethylcyclohexanol were prepared and their condensations attempted. The reduction of 2-anilinocarboxycyclohexanone[4] with lithium aluminum hydride afforded a mixture from which two 2-anilinomethylcyclohexanols, m.p. 80–82° and 102–104°, were isolated by repeated recrystallizations. However, acid treatment of these cyclohexanols did not lead to the formation of octahydrophenanthridines; that is, these alcohols were recovered unaffected by treatment with 90% sulfuric acid at room temperature; but, at 100°, each of these alcohols was converted to a mixture containing 7,8,9,10-tetrahydrophenanthridine[5] (I) as a main product.

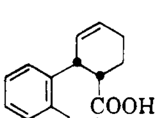
In 1951, Braude, *et al.*,[6] reported a synthesis of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine (II) of m.p. 72° which involved the Diels–Alder condensation of acrolein to *o*-nitrophenylbutadiene. Furthermore, they obtained two 2-(*o*-nitrophenyl)-1,2,5,6-tetrahydrobenzoic acids (III), m.p. 141° and 123°, by the addition reaction of the butadiene derivative with acrylic acid. The configurations of the acids were tentatively assigned as *trans* and *cis*, respectively, and those acids appeared to be appropriate intermediates for our purpose. The present re-examination of the reactions under various conditions showed that the acid of m.p. 141° was obtained at the reaction temperature of 50–80° and that of m.p. 123° at that of 150–160°. They gave the identical spectra in chloroform (not in Nujol), and the apparent discrepancy over the melting points of those acids was due to polymorphism. Catalytic hydrogenation of III in the presence of platinum smoothly gave hexahydrophenanthridone (IV), m.p. 207–208°, along with a small amount of an amino acid, $C_{13}H_{17}O_2N$, m.p. 144–145°. The lactam (IV) also was produced by esterification of III with diazomethane followed by hydrogenation. Reduction[7] of IV with lithium aluminum hydride resulted in formation of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine (V), m.p. 41–42°. Although the mixture melting point of the bases (II and V) was not depressed, their infrared spectra were different in both Nujol and chloroform, thus proving that V was a new stereoisomer.



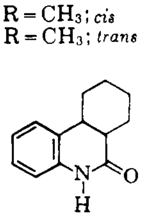
I



II, R = H; *trans*
V, R = H; *cis*
IX, R = CH_3; *cis*
XV, R = CH_3; *trans*



III



IV, *cis*
XIV, *trans*

If the new isomer (V) had the *cis* configuration, it was expected to be formed by catalytic hydrogenation[8]

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[1] Part XII of "The Condensed Polynuclear Perhydro-compounds Containing Nitrogen"; Part XI, T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **32**, 1005 (1959).

[2] T. Masamune, Y. Kubota, G. Homma, and M. Ohno, *J. Chem. Soc. Japan*, **77**, 1467 (1956).

[3] R. A. Barnes and A. D. Olin, *J. Am. Chem. Soc.*, **78**, 3830 (1956).

[4] B. K. Blount, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 1975 (1929); H. K. Sen and U. Basu, *J. Indian Chem. Soc.*, **6**, 309 (1929).

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[6] E. A. Braude and J. S. Fawcett, *ibid.*, 3113 (1951).

[7] *Cf.*, C. A. Grob and Hj. U. Schmid, *Helv. Chim. Acta*, **33**, 1955 (1950).

[8] For a recent and comprehensive review, see R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957).