An earlier preparation according to this method[3] gave impure fluoro ester, bp 24–30° (24 mm), in unspecified yield.

Methyl 4-Fluoro-3-oxo-2,2,4-trimethylpentanoate (4) from the Claisen Condensation of Methyl Sodioisobutyrate (2) and Methyl α-Fluoroisobutyrate (3).—Ethereal triphenylmethylsodium (100 ml, 9.7 mmol) was added slowly and with stirring to 0.80 g (7.8 mmol) of methyl isobutyrate (1) freshly distilled from calcium hydride. A stream of pure nitrogen was passed through the flask before and during the reaction. The red color was quickly discharged; only at the end of the addition did a persistent (15 min) red develop. To this enolate (2) solution, 0.90 g (7.5 mmol) of methyl α-fluoroisobutyrate (3) was added over a period of 5 min, and the mixtue was stirred at room temperature for 24 hr. A solution of acetic acid (1 ml) plus water (15 ml) was added; the aqueous layer was discarded; and the ether layer was first shaken with 10% aqueous sodium carbonate solution and then dried. Removal of solvent left a residue which on distillation afforded 0.73 g (51%) of water-white methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4), bp 77–79° (14 mm). The ir absorption curve for this material and that for the same material described above, both taken with neat liquids, were identical. The condensation product dissolved in deuteriochloroform showed nmr signals at 1.35 (6 H, s, 2,2-dimethyl), 1.48 [6 H, d, J = 21.5 Hz, $FC(CH_3)_2$], and 3.67 ppm (3 H, s, OCH_3).

Attempted Self-Condensation of Methyl Isobutyrate (1) with Methyl 3-Oxo-2,2,4-trimethylpentanoate (5). A. With Sodium Hydride.—A mixture of dry, freshly distilled methyl isobutyrate (46.3 g or 0.45 mol) and commercial sodium hydride (5.84 g or 0.24 mol) was boiled in an atmosphere of nitrogen for 4 hr. Hydrogen was evolved during the early stages of the reaction. The cooled mixture was poured over a mixture of concentrated sulfuric acid (20 ml) and crushed ice (100 g). The mixture was extracted with ether, and the ether solution was washed free of acid, dried, and warmed to remove solvent. Fractional distillation afforded 16 ml of unchanged starting material followed by about 11 ml of liquid, bp 80–110° (110–120 mm). Glpc revealed the presence of eight components. This product was not examined more closely.

B. With Triphenylmethylsodium.—Methyl isobutyrate (0.80 g or 7.8 mmol) was converted into its sodio derivative 2 exactly as described above in the condensation with methyl α-fluoroisobutyrate. Then, instead of the fluoro ester, 0.80 g of methyl isobutyrate (1) was added. The same treatment as before produced 1.3 g (81%) of unchanged starting material, bp 85–89°. The ir and the nmr spectra of the recovered material were the same as those from pure methyl isobutyrate.[9]

Other attempts at forming methyl 3-oxo-2,2,4-trimethylpentanoate (5) by Claisen condensation of methyl isobutyrate also failed.

Methyl 3-Oxo-2,2,4-trimethylpentanoate (5).—Diisopropyl ketone (10 ml of 0.091 mol) that had been distilled from calcium hydride was treated with 555 ml of a 0.138 M ethereal solution of triphenylmethylsodium (0.076 mol) until the red color persisted. The solution was poured over 50 g of solid carbon dioxode. The ether layer, rinsed with water and dried, was treated with excess ethereal diazomethane. Removal of solvent followed by two distillations of the residue gave 7.3 g (47%) of methyl 3-oxo-2,2,4-trimethylpentanoate (5), bp 93–94° (25 mm). By glpc this material contained less than 2% impurities.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.08; H, 9.35.

The neat liquid showed ir absorption peaks at 1720 and 1748 cm^{-1}.

Levine and Hauser, who employed the same method, but with sodium amide in place of triphenylmethylsodium, reported bp 93° (27 mm).[4]

Perchloryl Fluoride Fluorination of Methyl 3-Oxo-2,2,4-trimethyl pentanoate (5).—Methyl 3-oxo-2,2,4-trimethylpentanoate (5, 7.0 ml of 0.039 mol) was added in an atmosphere of nitrogen to 350 ml of a 0.10 M ethereal solution of triphenylmethylsodium (0.035 mol). The red color persisted for 10 min. An additional quantity of reagent was admitted (0.004 mol), and the mixture was allowed to stand for 30 min. Dry perchloryl fluoride was then bubbled through the orange solution. After 45 min, a drop of the reaction mixture in contact with water showed pH 5. Further treatment similar to that in the fluorination starting with methyl isobutyrate afforded 1.5 ml of distillate, bp 71° (6 mm), which by glpc contained at least 70% of methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4). The fluorine content of the mixture was low (7.84 instead of 9.99%) and the carbon content was high (58.76 instead of 56.83%). The ir absorption curve of this material was practically identical with that obtained before for 4.

Registry No.—1, 547-63-7; 3, 338-76-1; 4, 17555-86-1; 5, 918-71-8; perchloryl fluoride, 7616-94-6.

Cyclization and Rearrangement of Substituted Glyoxal Aldoxime Semicarbazones to 6-Substituted *as*-Triazine-3,5(2H,4H)-diones

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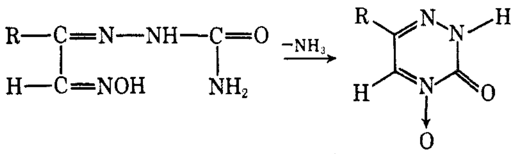
Received May 14, 1968

Cyclization of benzil monoxime guanylhydrazone nitrate to 2-imino-5,6-diphenyl-*as*-triazine 4-oxide, according to Scott and Reilly,[1] and the synthesis of 2-aminopyrazine 1-oxides by condensation of aminonitriles with substituted glyoxal aldoximes[2] are examples of the preparation of N-oxides from hydroximino compounds.

As a result of our attempts to prepare *as*-triazine derivatives (azapyrimidines) of pharmacological interest, it has been found that pyruvaldehyde aldoxime semicarbazone and arylglyoxal aldoxime semicarbazones undergo cyclization with loss of ammonia in boiling aqueous alkaline solutions.

From simple structural considerations the expected product would be 6-methyl- (or aryl-) *as*-triazine-3(2H)-one 4-oxide according to eq 1.



(1)

R = methyl or aryl

Physical properties and chemical reactions showed, however, that the compounds obtained are in fact the *as*-triazine-3,5(2H,4H)-diones identical with samples prepared by other methods.[3–5] Small amounts of nitriles (5–10%) and acids (10–20%) related to the starting materials were found as by-product. Thus benzonitrile was separated by steam distillation of the reaction mixture, and benzoic acid was extracted from the crude 6-phenyl-*as*-triazine-3,5(2H,4H)-dione.

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(9) Interestingly, Claisen condensation does occur when *ethyl* isobutyrate is treated with triphenylmethylsodium. *Cf.* C. R. Hauser and W. B. Renfrow, Jr., *ibid.*, **59**, 1824 (1937). Also *cf.* M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

(1) F. L. Scott and J. Reilly, *Chem. Ind.* (London), 907 (1952).

(2) W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951).

(3) J. Thiele and J. Bailey, *Ann.*, **303**, 75 (1898).

(4) S. Rossi, *Gazz. Chim. Ital.*, **83**, 133 (1953).

(5) J. Bougault, *Compt. Rend.*, **159**, 83 (1914).

TABLE I

PHENYLGLOXAL ALDOXIMES

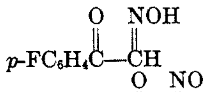
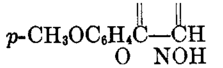
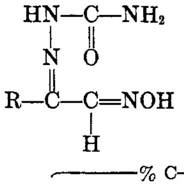
Formula	No.	% yield	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
 $p\text{-}FC_6H_4C(=O)CH=NOH$	1	60	128	57.48	57.12	3.59	3.66	8.38	8.18
 $p\text{-}CH_3OC_6H_4C(=O)CH=NOH$	2	65	118	60.33	60.44	5.02	4.97	7.82	8.18
 $p\text{-}CH_3C_6H_4C(=O)CH=NOH$	3	68	142	55.38	55.80	4.61	4.57	7.17	7.23

TABLE II

PHENYLGLYOXAL ALDOXIME SEMICARBAZONES



R	No.	% yield	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
$p\text{-}FC_6H_4$	1	95	181	$C_9H_9FN_4O_2$	48.21	48.36	4.01	3.91	25.00	25.25
$p\text{-}ClC_6H_4$	2	88	192	$C_9H_9ClN_4O_2$	44.90	45.11	3.73	3.63	23.28	23.41
$p\text{-}BrC_6H_4$	3	93	186	$C_9H_9BrN_4O_2$	42.18	42.25	3.15	3.20	19.64	19.92
$p\text{-}CH_3C_6H_4$	4	89	186	$C_{10}H_{12}N_4O_2$	54.54	54.60	5.45	5.41	25.45	25.19
$p\text{-}CH_3OC_6H_4$	5	85	180	$C_{10}H_{12}N_4O_3$	50.84	50.71	5.08	5.06	23.72	23.69
$p\text{-}CH_3SC_6H_4$	6	93	190	$C_{10}H_{12}N_4O_2S$	47.61	47.32	4.76	4.71	22.22	22.09
$p\text{-}NO_2C_6H_4$	7	86	223	$C_9H_9N_5O_4$	43.02	42.95	3.56	3.66	27.88	27.61

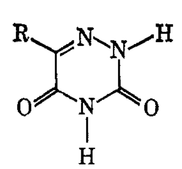
TABLE III

6-ARYL-*as*-TRIAZINE-3,5(2H,4H)-DIONES[a]

Aryl	No.	% yield	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
$p\text{-}FC_6H_4$	1	55	291	$C_9H_6FN_3O_2$	52.17	52.80	2.89	3.01	20.28	19.90
$p\text{-}ClC_6H_4$	2	48	279	$C_9H_6ClN_3O_2$	48.32	48.08	2.68	2.90	18.79	19.01
$p\text{-}BrC_6H_4$	3	45	298	$C_9H_6BrN_3O_2$	40.29	41.01	2.23	2.26	15.67	15.82
$p\text{-}CH_3C_6H_4$	4	67	275	$C_{10}H_9N_3O_2$	59.11	60.02	4.43	4.62	20.68	21.05
$p\text{-}OCH_3OC_6H_4$	5	54	273	$C_{10}H_9N_3O_3$	54.79	54.80	4.10	4.21	19.17	19.19
$p\text{-}CH_3SC_6H_4$	6	64	283	$C_{10}H_9N_3O_2S$	51.06	51.12	3.82	3.91	17.87	17.98
$p\text{-}NO_2C_6H_4$	7	65	293	$C_9H_6N_4O_4$	46.15	46.20	2.56	2.55	23.93	23.63

[a] All *as*-triazine derivatives prepared were subjected to infrared spectroscopy and show broad absorption in the region of 3–3.5 μ. C=O stretchings appear in the region of 5.75–5.95 μ as sharp strong doublets.

The reaction seems to be quite general. The following *as*-triazinediones have been prepared.



R = CH_3, C_6H_5, $p\text{-}FC_6H_4$, $p\text{-}ClC_6H_4$, $p\text{-}BrC_6H_4$, $p\text{-}CH_3C_6H_4$, $p\text{-}CH_3OC_6H_4$, $p\text{-}CH_3C_6H_4$, $p\text{-}NO_2C_6H_4$

It seems probable that formation of 6-methyl- (or aryl-) *as*-triazine-3(2H)-one 4-oxide is the first step of this cyclization and the oxygen atom of the N-oxide is transposed to the neighboring carbon atom to form a more stable product. The Wallach rearrangement[6] of azoxybenzenes to *p*-hydroxyazobenzenes is one of the earliest examples of transposition of N-oxide oxygen to form a hydroxyl group.

It has been shown recently[7] that 3-amino-*as*-triazine, treated with hydrogen peroxide, in acetic acid, "specific reagent for preparation of amine oxides," afforded 3-amino-5-hydroxy-*as*-triazine. 3-Amino-5,-6-dimethyl-*as*-triazine, under the same conditions, was oxidized to 3-amino-5-hydroxy-6-methyl-*as*-triazine, as a minor product. 3-Amino-5,6-dimethyl-*as*-triazine N-oxide was the major product.

We have successfully repeated the former reaction. 3-Amino-5-hydroxy-*as*-triazine was diazotized and gave *as*-triazine-3,5(2H,4H)-dione (azauracil) in 70% yield. This compound was also prepared by cyclization of glyoxylic acid semicarbazone[5] for comparison studies.

Attempts to prepare 3-hydroxy-6-alkyl- (or aryl-) *as*-triazine with no substitution at the 5 position, for further oxidation, failed.

Experimental Section[8]

Substituted Glyoxal Aldoximes.—Commercially available pyruvaldehyde aldoxime was used after recrystallization from aqueous methanol.

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[6] O. Wallach and L. Belli, *Ber.*, **13**, 525 (1880).

[7] T. Sazaki and K. Minamoto, *Chem. Pharm. Bull.* (Tokyo), **12**, 1329 (1964).

[8] Melting points are corrected and were determined on a Kofler hot table microscope. The infrared spectra were determined with a Leitz Model III spectrograph, using potassium bromide disks.

New phenylglyoxal aldoximes were prepared following procedures for the known compounds in this series.[9,10] The properties of the new phenylglyoxal aldoximes are described in Table I.

We have observed that in all cases different amounts of corresponding substituted benzoic acids appeared as by-products. The crude compounds were washed with an excess of 5% cold solution of sodium bicarbonate, which dissolved all free acid present. Analytical samples were prepared by recrystallization in diluted ethyl alcohol.

Substituted Glyoxal Aldoxime Semicarbazones.—Pyruvaldehyde aldoxime semicarbazone[11] and phenylglyoxal aldoxime semicarbazone[12] are known compounds. New phenylglyoxal aldoxime semicarbazones were prepared according to the Dey procedure[12] by interaction of corresponding phenylglyoxal aldoximes with equimolecular quantities of semicarbazide hydrochloride and sodium acetate dissolved in a minimum quantity of 50% ethyl alcohol at 50°. The solvent of recrystallization was also 50% ethyl alcohol. The physical data of semicarbazones obtained are summarized in Table II.

***as*-Triazine-3,5(2H,4H)-dione (Azauracil).**—3-Amino-5-hydroxy-*as*-triazine,[7] 2.25 g (0.02 mol) in 10 ml of concentrated hydrochloric acid and 10 ml of water, was treated with a concentrated solution of 1.5 g (0.022 mol) of sodium nitrite, below 5°. The solution was shaken occasionally during 3 hr standing at room temperature, after which pure azauracil crystallized out. A further quantity can be obtained by concentration of the mother liquor. The yield was 70%, mp 283° (water) (lit.[8] mp 272°). Mixture melting point with a specimen of the same compound prepared with a 15% yield by cyclization of glyoxylic acid semicarbazone[5] was not depressed.

6-Methyl-*as*-triazine-3,5(2H,4H)-dione (Azathymine).—A suspension of pyruvaldehyde aldoxime semicarbazone, 7.20 g (0.05 mol) in 40 ml of water, was refluxed for 20 hr with 7 g (0.05 mol) of anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the refrigerator was removed each 3 hr by circulating water through it. Finally, the solution was charcoaled, acidified with hydrochloric acid, and evaporated until dry on a steam bath. The dry residue was extracted in a Soxhlet apparatus with ethyl acetate. The solvent was distilled off, and the residue was recrystallized in water to give 2.1 g (36%), mp 216° (lit.[13] mp 212°). The infrared spectrum of the compound obtained was identical with the spectrum of a specimen prepared by another method.[13]

6-Phenyl-*as*-triazine-3,5(2H,4H)-dione.—Phenylglyoxal aldoxime semicarbazone,[12] 2 g (0.01 mol) in 25 ml of water, was refluxed for 8 hr with 2.76 g (0.02 mol) of the anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the course of reaction in the condenser was removed occasionally by washing the condenser. The solution was charcoaled and acidified with concentrated hydrochloric acid to give a white crystalline powder. The yield was 1.2 g (64%), mp 262° (from diluted alcohol) (lit.[5] mp 262°).

When the same reaction was conducted with sodium bicarbonate instead of potassium carbonate a 25% yield was obtained.

Substituted 6-phenyl-*as*-triazine-3,5(2H,4H)-diones were prepared by cyclization of the corresponding phenylglyoxal aldoxime semicarbazones according to the above method. The properties of the compounds obtained are summarized in Table III.

Registry No.—Table I—1, 17628-74-9; 2, 1823-76-3; 3, 17628-76-1; Table II—1, 17628-77-2; 2, 17628-78-3; 3, 17628-79-4; 4, 17628-80-7; 5, 17628-81-8; 6, 17628-82-9; 7, 17628-83-0; Table III—1, 17629-10-6; 2, 17629-11-7; 3, 17629-12-8; 4, 17629-16-2; 5, 17629-17-3; 6, 17629-18-4; 7, 17629-19-5.

Acknowledgment.—The author wishes to thank Professor N. Sharghi for his constant encouragement and the Central Treaty Organization for provision of essential materials.

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(9) L. Claisen, *Ber.*, **20**, 655 (1887).

(10) W. Borsche, *ibid.*, **62**, 1360 (1929).

(11) H. Rupe and S. Kessler, *ibid.*, **42**, 4715 (1909).

(12) B. B. Dey, *J. Chem. Soc.*, **105**, 1039 (1914).

(13) K. Chang Pauline, *J. Org. Chem.*, **23**, 1951 (1958).

Fischer Indole Synthesis. Direction of Cyclization of Isopropylmethyl Ketone Phenylhydrazone

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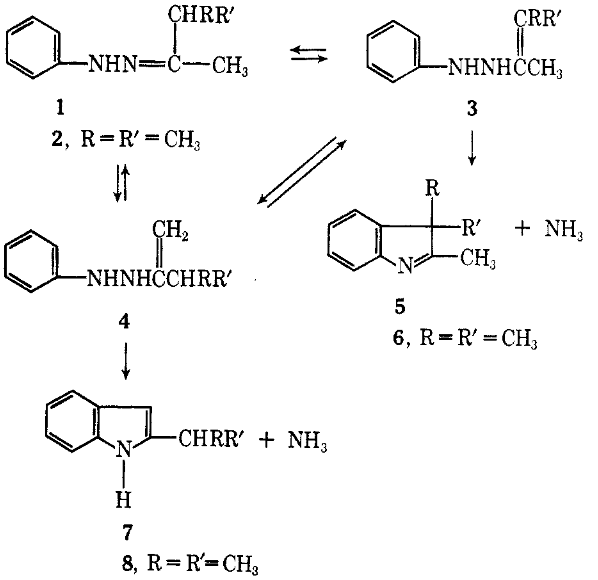
Plancher obtained 2,3,3-trimethylindolenine (2,3,3-trimethylpseudoindole) (**6**) by treating isopropylmethyl ketone phenylhydrazone (**2**) with zinc chloride in alcohol.[1] After observing the reactions of other phenylhydrazones (**1**), he established the rule that ketone arylhydrazones containing the group —NHN=C(CH$_3$)CH< cyclize exclusively at the tertiary carbon atom to give 2-methylindolenines (**5**).[2] More recent reports have shown that the direction of ring closure of unsymmetrical methyl ketone phenylhydrazones is dependent on the nature of the acid catalysts.[3-5] This dependence has been attributed to shifts in the equilibrium (**3** $\rightleftharpoons$ **4**)[4] and, more specifically, to steric interactions in the transition state which are affected by the size of the acid.[5] See Scheme I.

SCHEME I



We wish to report another interesting exception to Plancher's rule. The phenylhydrazone **2** cyclizes to give both the indolenine **6** and 2-isopropylindole **8**, with the product ratio depending on the strength and amount of acid catalyst. Thus, the product ratio (**6**:**8**) decreases from 95:1 with dilute H$_2$SO$_4$ to 0.15:1 with 6 mol of 78% H$_2$SO$_4$. This is the first recorded case in which both directions of cyclization have been obtained by varying the concentration and amount of one catalyst. Weak acids give **6** exclusively. The results are given in Tables I and II. Samples of 2,3,3-tri-

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(1) G. Plancher, *Ber.*, **31**, 1496 (1898).

(2) G. Plancher and A. Bonavia, *Gazz. Chim. Ital.*, **32**, 418 (1902).

(3) For a thorough review of the Fischer indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 387 (1963).

(4) N. P. Buu-Hoi, P. Jacquignon, and D. Perin-Roussel, *Bull. Soc. Chim. Fr.*, 2849 (1965).

(5) R. E. Lyle and L. Skarlos, *Chem. Commun.*, **18**, 644 (1966).