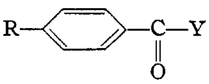
TABLE I

KETONES OF FORMULA



$R-C_6H_4-C(=O)-Y$

R[a]	Y	Iodine, g.	Reflux time, hr.	Method	Yield,[b] %	M.p., °C.	B.p. °C.	B.p. Mm.
OCH_3 (1:2)	*p*-Anisyl	7.7	15	A	84	142–144[c]		
H (0.5:1)	*p*-Xenyl	15.0	14	B	50	102–103[d]	156–158	0.1
Cl (1.1:1)	*p*-Anisyl	25	15	A	93	124–125		
NO_2 (1:2)	*p*-Anisyl	40	15	B	57	126–128[e]	192–194	0.9
H (1.1:1)	Veratryl	2	15	[f]	81[g]	102–103[h]	162–170	2.0
H (0.5:1)	2-Mesityl	20	10	B	65		141–143[i]	0.03
H (1:2)	*p*-Ethoxyphenyl	8	15	B	83[j]		129[j]	0.6
H (1:1.5)	2-Methoxynaphthyl	15	7.5	B	72	124–125[k]	200–205	2.0
OCH_3 (1:2)	2-Thienyl	2	8	A	76[l]	76–77		
Cl (1:1)	2-Thienyl	6	8	A	50[m]	99.5–100[m]		
H (1:1)	2-(5-Chlorothienyl)	20	9	A	34[n]	63–64[k]		
Cl (1:1)	2-(5-Chlorothienyl)	20	15	A	58	105–106[o]		

[a] Figures in parentheses refer to mole ratios of reactants, the first number representing the moles of acylating agent, *p*-R—C_6H_4COCl. [b] All compounds were recrystallized from isopropyl alcohol unless otherwise stated. [c] H. Schnackenberg and R. Scholl, *Ber.*, **36**, 654 (1903), using aluminum chloride, reported no yield. [d] L. Long and H. Henze, THIS JOURNAL, **63**, 1939 (1941), obtained a 75% yield with aluminum chloride as condensing agent. [e] *Anal.* Calcd. for $C_{14}H_{11}NO$: N, 5.45. Found: N, 5.38. N. Böeseken, *Rec. trav. chim.*, 19, 25 (1900), found a melting point of 121°. [f] At the end of the reflux period, the reaction mixture was distilled *in vacuo*. [g] A small amount (2.3 g.) of a higher boiling fraction, b.p. 207–210° (0.04 mm.), was also obtained. This presumably dibenzoylated veratrole gave a mono-2,4-dinitrophenylhydrazone which melted at 190–191° after recrystallization from ethanol. *Anal.* Calcd. for $C_{28}H_{24}N_2O_4$: C, 63.86; H, 4.07. Found: C, 63.04; H, 3.93. [h] Recrystallized from hexane. B. König and St. V. Kostanecki, *Ber.*, **39**, 4027 (1906), gave no yield for their product. [i] P. J. Montagne, *Rec. trav. chim.*, **27**, 327 (1908). [j] Although C. Torres, *Anales soc. españ. fís. quím.*, **24**, 82 (1926); *C. A.*, **20**, 2158 (1926), reported that the oxime of his product melted at 135–136°, the ketoxime melted at 151–152° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.53; H, 6.21. [k] Recrystallized from heptane. [l] Employing equimolecular quantities of the reactants, the product was obtained in 62% yield. *Anal.* Calcd. for $C_{12}H_{10}O_2S$: S, 14.65. Found: S, 14.28. The compound has recently been prepared by Ng. D. Buu-Hoï, Ng. Hoán and Ng. D. Xuong, *Rec. trav. chim.*, **69**, 1083 (1950), in 80% yield. [m] The yield dropped to 35% when 2.0 g. of iodine was employed. The product was recrystallized from hexane. There was also isolated 13.0 g. of di-(4-chlorobenzoyl)-thiophene, m.p. 238–239° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for $C_{18}H_{10}Cl_2O_2S$: Cl, 19.62. Found: Cl, 19.38. Buu-Hoï and co-workers (*cf.* preceding reference) obtained a 71% yield of 2-(4-chlorobenzoyl)-thiophene. [n] *Anal.* Calcd. for $C_{11}H_7ClOS$: C, 59.32; H, 3.06; Cl, 15.95. Found: C, 59.24; H, 3.17; Cl, 15.95. Buu-Hoï, Hoán and Xuong [*cf.* note (*l*)] reported a 53% yield. [o] *Anal.* Calcd. for $C_{11}H_6Cl_2OS$: C, 51.38; H, 2.35; Cl, 27.58; S, 12.47. Found: C, 51.48; H, 2.44; Cl, 27.40; S, 12.43. The conventional Friedel–Crafts procedure [*cf.* note (*l*)] afforded a 77% yield.

Reaction of N,N-Dimethylaniline with Benzoyl Chloride.—A solution of 20.0 g. of iodine, 70.3 g. (0.50 mole) of benzoyl chloride and 121.2 g. (1.0 mole) of N,N-dimethylaniline was refluxed for 10 hours, cooled, washed with dilute sodium hydroxide, dried over anhydrous potassium carbonate and distilled *in vacuo*. The yellow oil, b.p. 189° (0.9 mm.), weighing 45.0 g., crystallized on cooling and was recrystallized from hexane. The white crystals, m.p. 164–165°, showed no depression in melting point on admixture with an authentic sample of benzanilide.[11]

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.18; H, 5.57; N, 7.30. Found: C, 79.23; H, 5.58; N, 7.13.

In a similar manner there was obtained 35.3 g. of a red oil, b.p. 121° (1.0 mm.), from a mixture of 24.2 g. (0.20 mole) of the tertiary amine, 42.2 g. (0.30 mole) of benzoyl chloride and 0.8 g. of iodine. The amide, crystallized from heptane and recrystallized to constant melting point from the same solvent, melted at 63.5–64.5°.[11]

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.13. Found: C, 79.54; H, 6.28; N, 6.24.

Hydrolytic cleavage with hydrochloric acid[11] afforded benzoic acid, identified by the fact that its melting point was not depressed when mixed with an authentic sample, and N-methylaniline, identified similarly as its hydrochloride, m.p. 121–123°.

Reaction of N,N-Dimethylaniline with Iodine.—A mixture of 24.2 g. (0.2 mole) of N,N-dimethylaniline and 8.0 g. of iodine, refluxed for 3 hours, deposited, by sublimation in an air condenser during the reflux period, 6.0 g. of the methiodide of N,N-dimethylaniline, m.p. 213–214°. Mixed with an authentic sample, there was no depression in melting point.

Anal. Calcd. for $C_9H_{14}IN$: C, 41.22; H, 5.34. Found: C, 40.99; H, 5.35.

Benzylation of Anisole.—From a mixture of 32.4 g. (0.3 mole) of anisole, 18.9 g. (0.15 mole) of benzyl chloride and 6.0 g. of iodine, refluxed 14 hours, there was isolated (Method B) 15.0 g. (51%) of a yellow oil, b.p. 106–108° (0.04 mm.). A sample of the distillate, after hydrobromic acid demethylation, yielded *p*-benzylphenol, m.p. 84.5–85.5°.[12]

There was also obtained 9.6 g. (22%) of a higher boiling fraction, b.p. 165–167° (0.09 mm.), presumed to be 2,4-dibenzylanisole.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.04; H, 6.67.

From mixtures of 1.0 mole of thiophene or 2-chlorothiophene, 0.5 mole of benzyl chloride and 7.5 g. of iodine which were refluxed 14 hours, only starting materials could be recovered.

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(11) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Company, New York, N. Y., 1947, pp. 185, 403 and 413.

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd edition, 1948, p. 272.

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Use of 2-Aminopyridine in the Voigt Reaction

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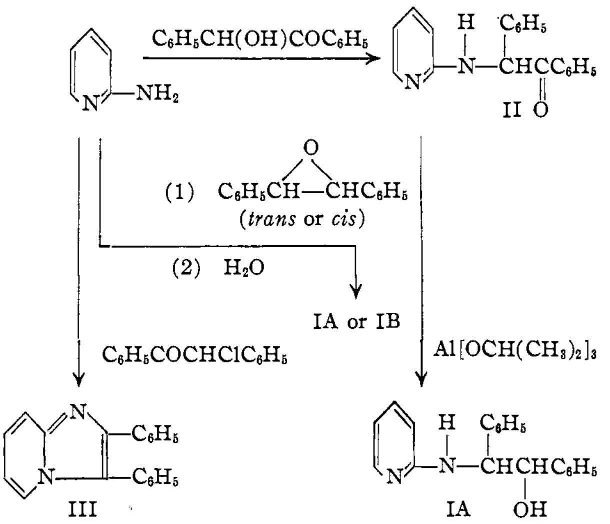
RECEIVED SEPTEMBER 18, 1952

The synthesis of the two stereochemical isomers of N-(2-pyridyl)-1,2-diphenyl-2-aminoethanol (I) was desired as part of a program involving the preparation for antimitotic evaluation of a number of N-substituted compounds related to 1,2-diphenylethylamine.[1,2] The products were obtained from, and their stereochemical configurations assigned[3,4] on the basis of, the reaction between 2-aminopyridine and the isomeric stilbene oxides in the presence of lithium amide. The *erythro*-aminoalcohol (IA) (from *trans*-stilbene oxide) was more satisfactorily prepared by aluminum isopropoxide reduction of N-(2-pyridyl)-desylamine (II). The preparation of the latter from 2-aminopyridine and benzoin represents an extension of the Voigt reaction to a heterocyclic amine containing a nitrogen–carbon–nitrogen system. This does not appear to be general, however, in view of the failure of 2-benzylaminopyridine, 2-aminopyrimidine, 2-aminothiazole or 2-aminolepidine to react.

Heating a mixture of 2-aminopyridine with desyl chloride gave the cyclized product (III), 2,3-diphenylimidazo[1,2-a]pyridine, instead of the desired ketone (II).



Experimental[5]

Intermediates.—α-Phenylcinnamic acid, m.p. 163–167°, was prepared in 73% yield by the method of Buckles and Hausman[6] and purified by acidification of its ether-washed alkaline solution. Decarboxylation, by refluxing a quinoline solution of the compound in the presence of copper chromite[7] for 3 hours instead of the recommended 1.5 hours,[8] gave an 80% yield of *cis*-stilbene, b.p. 128–135° (2 mm.), and a 7% yield of *trans*-stilbene, m.p. 121–123°. The latter was better obtained by reduction of benzoin.[9,10] The stilbene oxides were prepared by the procedure for styrene oxide.[11] *cis*-Stilbene oxide,[8] b.p. 126–132° (4 mm.), was isolated in 72% yield, after a reaction time of 40 hours; the *trans* isomer,[3] m.p. 64–67°, obtained in 80% yield, required 134 hours.

Benzoylcarbinol, prepared from phenacyl bromide by the potassium formate method of Julian, *et al.*,[12] for the synthesis of α-hydroxy-β-phenylpropiophenone, was obtained in 72% yield, m.p. 89.5–90.5°.[13]

Anal. Calcd. for $C_8H_8O_2$: C, 70.60; H, 5.93. Found: C, 70.64; H, 5.96.

***threo*-N-(2-Pyridyl)-1,2-diphenyl-2-aminoethanol (IB).**—A mixture of 4.75 g. (0.05 mole) of 2-aminopyridine, 10.8 g. (0.055 mole) of *cis*-stilbene oxide, 1.3 g. of 98% lithium amide and 100 ml. of dry toluene was refluxed for 24 hours. On treating the cooled reaction mixture with ice-water, a precipitate appeared. This was separated by filtration, washed with water and air-dried. The tan powder weighed 8.5 g., m.p. 170–175°. An additional 0.35 g. of product, m.p. 168–173°, obtained by concentrating the toluene solution, raised the yield to 61%. The melting point remained constant at 177.5–178.5° after three recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25. Found: C, 79.02; H, 6.51.

N-(2-Pyridyl)-desylamine (II).—A mixture of 63.7 g. (0.3 mole) of benzoin, 31.0 g. (0.33 mole) of 2-aminopyridine, 200 ml. of toluene and 6 ml. of concd. hydrochloric acid was refluxed for 20 hours; the water separating during the reaction was collected in a moisture trap. After cooling to room temperature, a small amount of an unidentified yellow solid was removed by filtration. The solvent was removed from the filtrate by a vacuum distillation and the oily residue crystallized by rubbing with hexane. The orange-yellow solid, m.p. 79–91°, weighing 72.1 g. (83%) after air-drying, was recrystallized four times from isopropyl alcohol, m.p. 106–108°.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.57; H, 5.60; N, 9.68.

***erythro*-N-(2-Pyridyl)-1,2-diphenyl-2-aminoethanol (IA).**—From 86.5 g. (0.3 mole) of N-(2-pyridyl)-desylamine and 121.4 g. of a 50% solution of aluminum isopropoxide in 400 ml. of dry isopropyl alcohol[14] there was obtained 83 g. (95%) of crude product which melted at 156.5–157.5° after five recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.61; H, 6.28; N, 9.82.

This isomer was also obtained, in 65% yield, but less conveniently, by lithium aluminum hydride reduction[15] of the aminoketone, m.p. 154–156°. From *trans*-stilbene oxide, by the method described for the preparation of the *threo*-aminoalcohol (IB), there was obtained a 50% yield of crude product which melted at 154–156° after two recrystallizations from isopropyl alcohol. There was no depression in melting point on admixture with product prepared by either the aluminum isopropoxide or lithium aluminum hydride reduction of the aminoketone.

2,3-Diphenylimidazo[1,2-a]pyridine (III).—A mixture of 11.5 g. (0.05 mole) of desyl chloride[16] and 14.1 g. (0.15 mole) of 2-aminopyridine was heated in an oil-bath maintained at 110–120° for three hours. The melt was dissolved in benzene. The solution was washed with water and the solvent then removed by distillation. The oily residue, crystallized by rubbing with hexane, was recrystallized from isopropyl alcohol. The product weighed 5.10 g. (38%), m.p. 145–150°. The melting point remained constant at 151.5–153° after two further recrystallizations from isopropyl alcohol.

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(1) I. A. Kaye and C. L. Parris, *J. Org. Chem.*, **16**, 1859 (1951).

(2) I. A. Kaye and C. L. Parris, THIS JOURNAL, **74**, 1566 (1952).

(3) R. E. Lutz, J. A. Freek and R. S. Murphey, *ibid.*, **70**, 2015 (1948).

(4) R. E. Lutz and R. S. Murphey, *ibid.*, **71**, 478 (1949).

(5) Melting points are corrected, boiling points are not.

(6) R. E. Buckles and E. A. Hausman, THIS JOURNAL, **70**, 415 (1948), and R. E. Buckles, M. P. Bellis and W. D. Coder, Jr., *ibid.*, **73**, 4972 (1951).

(7) W. A. Lazier and H. R. Arnold in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 142.

(8) T. W. J. Taylor and C. E. J. Crawford, *J. Chem. Soc.*, 1130 (1934). The reference in note 28(a) of ref. (3) to this publication for the preparation of *cis*-stilbene oxide is in error.

(9) R. L. Shriner and A. Berger in *Org. Syntheses*, **23**, 86 (1943).

(10) A sample of benzoin was generously supplied by the Heyden Chemical Corp.

(11) H. Hibbert and P. Burt, in "Organic Syntheses," Coll. Vol. I, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 494.

(12) P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, THIS JOURNAL, **67**, 1203 (1945).

(13) G. R. Cebrián, *Anales real soc. españ. fís y quím.*, *Ser. B*, **44**, 587 (1948); *C. A.*, **42**, 8176 (1948), obtained a 60% yield by the conventional potassium acetate procedure.

(14) A. L. Wilds in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, chapter 5.

(15) W. G. Brown in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, chapter 10.

(16) A. M. Ward in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.77; H, 5.17; N, 10.14.

Under milder conditions, cyclization also occurred when phenacyl bromide was used in place of desyl chloride. Using the procedure of Julian, *et al.*, for the preparation of α-anilinopropiophenone[12] there was obtained a quantitative yield of 2-phenylimidazo[1,2-a]pyridine, m.p. 135–136°, after two recrystallizations from hexane. With sodium carbonate or sodium acetate replacing the sodium bicarbonate in this procedure, the yield dropped to 88 and 33%, respectively.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19. Found: C, 80.14; H, 5.34.

The picrate melted at 236–238° after two recrystallizations from acetone.[17]

Anal. Calcd. for $C_{13}H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 53.90; H, 3.10. Found: C, 54.39; H, 3.06.

Reaction of 2-Aminopyridine with Benzoylcarbinol.—In an effort to gain additional insight into the mechanism of the Voigt reaction,[3,12] benzoylcarbinol was treated with 2-aminopyridine. Using the procedure employed in the preparation of N-(2-pyridyl)-desylamine (II), there was obtained from 13.6 g. (0.1 mole) of benzoylcarbinol, 10.3 g. (0.11 mole) of 2-aminopyridine, 100 ml. of toluene and 2 ml. of concd. hydrochloric acid, 5.5 g. of a pale yellow solid, b.p. 142–144° (10 mm.). The compound melted at 150° after two recrystallizations from isopropyl alcohol and showed no depression in melting point when mixed with an authentic sample of 2-aminopyridine benzoate melting at 152–153°.

Anal. Calcd. for $C_3H_6N_2 \cdot C_7H_6O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.17; H, 5.42; N, 12.82.

The picrate of the free base melted at 216–218°. No depression in melting point was observed on admixture with an authentic sample of 2-aminopyridine picrate.[18]

Acknowledgment.—This investigation was supported by a research grant from the National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service.

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[17] N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951). The picrate of their cyclized product, m.p. 228–229°, did not give a satisfactory nitrogen analysis.

[18] W. Marckwald, *Ber.*, **27**, 1317 (1894).

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Reactions of Acrolein and Related Compounds. VIII. Preparation of Sultones

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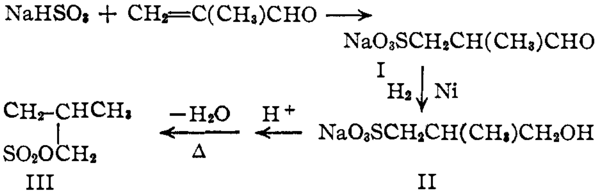
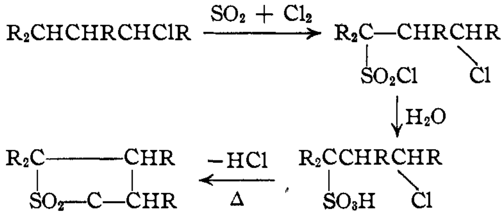
RECEIVED SEPTEMBER 16, 1952

A novel and convenient synthesis of the known and highly reactive 3-hydroxy-2-methyl-1-propanesulfonic acid sultone hereinafter called β-methyl-γ-propanesultone (III) has been realized and may be outlined as



The over-all yield of sultone based on methacrolein was 73%.

Several aliphatic γ-sultones have been previously prepared by Helberger[1,2] and by Asinger[3] and their associates. The method used by these workers involved sulfochlorination of alkyl halides as shown in the scheme



The aliphatic γ-sultones have been shown[1,4] to undergo readily a wide variety of reactions.

Earlier attempts by Marckwald and Frahne to synthesize 3-hydroxy-1-propanesulfonic acid sultone, γ-propanesultone, were unsuccessful.[5] They added bisulfite to acrolein and to allyl alcohol and reduced the acrolein adduct with potassium amalgam presumably to the 3-hydroxy-1-propanesulfonate, but were unable to complete the conversion to the sultone.

In the present process a slight excess (2%) of methacrolein was added to the aqueous solution of sodium bisulfite with the view of removing as completely as possible any bisulfite which might poison the catalyst in the subsequent hydrogenation. The resultant solution was hydrogenated directly over Raney nickel. Saturation of the concentrated reaction mixture with hydrogen chloride resulted in the precipitation of sodium chloride which was removed by filtration. Removal of solvent from the filtrate left a light yellow, viscous oil which on distillation under reduced pressure gave the known[3] β-methyl-γ-propanesultone (III).

The fact that water and not hydrogen chloride was eliminated during this distillation establishes the fact that no significant amount of the hydroxy acid was converted to the chloroacid during treatment with hydrochloric acid.

β-Methyl-γ-propanesultone also has been prepared through the peroxide-catalyzed addition of sodium bisulfite to methallyl alcohol. The yield of sultone based on methallyl alcohol charged was 52%. Probably the reason the yield is lower here than from methacrolein is that in this latter case the initial addition proceeded to only about 88% conversion.

Preparations of γ-propanesultone were carried out from acrolein and from allyl alcohol by procedures identical with the above. The melting point of the product was in agreement with that given by Helberger.[1] The yield from acrolein was 16% while that from allyl alcohol was only 5%.

In addition to the conversion of the aldehyde group of the bisulfite adduct of methacrolein to a

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[1] J. H. Helberger, *Reichsamt Wirtshaftaufbau Chem. Br. Pruf. Nr.*, **15**, (U. S. Office of Publication Board, P.B. 52013) 269 (1942); *C. A.*, **41**, 4101 (1947).

[2] J. H. Helberger, G. Manecke and H. M. Fischer, *Ann.*, **562**, 23 (1949); *C. A.*, **43**, 6569 (1949).

[3] F. Asinger, F. Ebeneder and H. Eckholdt, U. S. Office of Publication Board, P.B. 70183, Frame 893.

[4] J. H. Helberger, G. Manecke and R. Heyden, *Ann.*, **565**, 22 (1949).

[5] W. Marckwald and H. H. Frahne, *Ber.*, **31**, 1854 (1898).