cal quantity of hydrogen at an average pressure of 1000 lb. per sq. in. was absorbed in three hours at 78°. After filtration of the catalyst the brown reaction product was fractionally distilled. The first fraction, dimethylaminoethylamine, distilled at 105–108° and weighed 62 g. (47%). It fumed on exposure to air.

The **phenylthiourea** melted at 82.6–83.0°; reported,[2] 83.0–83.5°.

bis-(β-Dimethylaminoethyl)-amine.—After the distillation of dimethylaminoethylamine the second fraction, which distilled at 198° as a light yellow, hygroscopic liquid, weighed 24 g. (20%). After drying over potassium hydroxide and redistilling, the product was clear and colorless; d^{25} 0.8283; $n^{25}D$ 1.4406; *MR* 50.74 (calcd.), 50.62 (obs.).

Anal. Calcd. for $C_8H_{21}N_3$: C, 60.32; H, 13.29; N, 26.38. Found: C, 59.60; H, 13.52; N, 26.66.

The **phenylthiourea,** prepared with phenyl isothiocyanate in benzene solution, melted at 113.6–114.0°.

Anal. Calcd. for $C_{15}H_{26}SN_4$: C, 61.18; H, 8.90. Found: C, 61.15; H, 8.87.

Summary

Dimethylaminoacetonitrile has been synthesized from dimethylamine solution in good yield. By catalytic hydrogenation of this nitrile dimethylaminoethylamine has been prepared.

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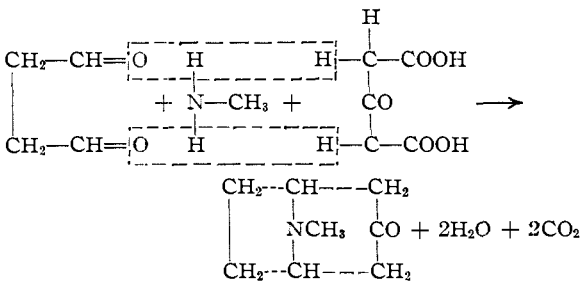
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

Tropanone and its Homologs

BY LEROY C. KEAGLE[1] AND WALTER H. HARTUNG

Robinson's synthesis of tropanone[1a] from acetone, methylamine and succinaldehyde, characterized by Willstätter as "von bewundernswerter Eleganz,"[2] stimulated speculation on the possible mechanism of synthesis of atropine and other products in plant tissue. The discussion, well summarized by Schopf,[3] raises among others the question whether certain natural intermediates, which may be expected to occur in living tissue, react spontaneously to give the precursors of natural products. If so, then those same intermediates brought together *in vitro*, under biological conditions of temperature, dilution and *p*H, should react to form those same precursors. These, by further biochemical processes in the plant, *e. g.*, by hydrogenation, decarboxylation, esterification, etc., are converted into the natural products.

Robinson's synthesis of tropanone does not meet biological conditions, for his reaction proceeded only in strongly alkaline solution. However, if, instead of acetone, acetonedicarboxylic acid is employed, the formation of tropanone proceeds smoothly according to the equation



The yields are highly satisfactory at high dilution and in neutral or nearly neutral solution.[3,4] Reduction of this ketone in the plant with subsequent esterification by tropic acid leads to atropine or, if the acid is optically active, to hyoscyamine.

Analogous syntheses have been postulated and demonstrated as possible and probable for other alkaloids, including those derived from quinoline, isoquinoline, pyridine, etc. (*cf.* ref. 3).

Such hypotheses are intriguing. Not only do the experimental results offered in their favor merit confirmation, but further questions naturally follow: First, may these postulated reactions be adapted practically for the synthetic preparation of natural products? Second, may the reaction be modified, *e. g.*, by employing other intermediates, for the synthesis of substances unknown in nature but with modified physiological properties? The results reported here give partial affirmative answers to both questions, with respect to tropanone and its homologs.

Not only have the experiments of Schöpf and Lehmann,[4] in their synthesis of tropanone under biological conditions, been substantially confirmed, but also the conditions of the condensation reaction may be appreciably modified to make it more practicable in the laboratory. The reaction also has been extended by substituting other primary amines for methylamine to obtain, in an analogous manner, higher homologs, with the larger alkyl groups attached to the nitrogen atom of the tropanone skeleton. Since tropanone may be easily reduced to tropanol, no difficulty is anticipated in preparing the N-homologs.

Of the necessary intermediates succinaldehyde is the most difficult to obtain. Saytzeff[5] reduced succinyl chloride with sodium amalgam, but his product was later shown to be γ-butyrolactone.[6] The dialdehyde was prepared in small yields

(1) H. A. B. Dunning Fellow 1940–1943. Present address: Rutgers University, College of Pharmacy, Newark, N. J.

(1a) Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

(2) Winterstein-Trier, "Die Alkaloide," Gebrüder Borntraeger, Berlin, 1931, p. 295.

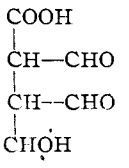
(3) Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937).

(4) Schöpf and Lehmann, *Ann.*, **518**, 5 (1935).

(5) Saytzeff, *Ber.*, **6**, 1255 (1873); **13**, 1061 (1880).

(6) Fittig, *Ann.*, **208**, 112 (1881).

directly by the ozonolysis of cyclooctadiene[7] or of diallyl,[8] or by the decarboxylation of the dicarboxylic acid derivative[9]



which intermediate was synthesized *via* the Claisen condensation from ethyl formate and ethyl succinate. The tetraethyl acetal, $(C_2H_5O)_2CH\text{-}CH_2CH_2CH(OC_2H_5)_2$, was obtained by the electrolysis of the potassium salt of the acetal of glyoxalic acid,[10] and also by allowing ethylmagnesium bromide to react on ethyl formate and acetylene.[11] The dioxime, prepared by various investigators, is apparently the best-known derivative; it has been prepared by the reduction of 1,4-dinitrobutane[12]; but a more widely used procedure was to allow hydroxylamine hydrochloride, in the presence of alkali, to react with pyrrole.[13] The dioxime, reacting with nitrogen trioxide[13b] or with ethyl nitrite[13d] formed the free aldehyde. Succinaldehyde is reported to polymerize readily, but on distillation the monomer re-forms.[14] A good synthesis is still desirable.

Experimental

Succinaldehyde.—Various procedures, usually applicable for the preparation of aldehydes from appropriate intermediates, were tried unsuccessfully: *e. g.*, the distillation of mixed calcium succinate and calcium formate; a Rosenmund type of reduction of succinyl chloride; the partial hydrogenation of succinonitrile, either catalytically or by Stephen's method[15] with stannous chloride, to the diimine; all gave no trace of the desired aldehyde. Bromo- and chloroacetal do not undergo the Fittig condensation, but instead yield ethyl vinyl ether.[16] The Grignard condensation of β-halogenopropionaldehyde acetal with ethyl orthoformate, expected to yield the tetraethyl acetal of succinaldehyde, was not tried since neither β-chloro- nor β-bromopropionaldehyde acetal would react with magnesium. Hence, resort was made to the synthesis of succinaldehyde from pyrrole, *via* the dioxime, and a procedure was employed which does not require the isolation of the dialdehyde.

Succinaldoxime was prepared substantially after the manner of Willstätter and Heubner.[13c] In a 2-liter, 3-necked flask, equipped with mechanical stirrer and reflux condenser, were placed 1 liter of ethanol, 67 g. freshly distilled pyrrole, and 141 g. hydroxylamine hydrochloride.[17a] The mixture was stirred and heated to refluxing; as soon as solution was complete, 106 g. anhydrous sodium carbonate was added, in small portions, as rapidly as possible; and the solution was then refluxed for twenty-four hours. The hot alcoholic mixture was then filtered to remove sodium chloride, and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in the minimum of boiling water, the solution heated with decolorizing charcoal, filtered and the product allowed to crystallize in the refrigerator. Additional product could be obtained by concentrating the mother liquors. The yield of dioxime varied from 40 to 44 g., 35 to 38%, and the product melted at 171–172°.

A twentieth mole, 5.8 g., of succinaldoxime was placed in a beaker of 250 ml. capacity and 54 ml. of 10% sulfuric acid was added. The mixture was cooled to 0° and to it was added, in small portions, 7.0 g. of sodium nitrite, keeping the temperature at 0°. Evolution of nitrogen dioxide fumes indicates too rapid addition of the nitrite. The dioxime was now completely dissolved, and the solution was allowed to warm slowly to 20° and effervescence to go to completion. The lemon-colored solution was then neutralized to litmus by the addition of small portions of barium carbonate, and the precipitated barium sulfate was removed, leaving the free succinaldehyde in the filtrate. The solution was assayed at this point by precipitating quantitatively from an aliquot portion the bis-2,4-dinitrophenylhydrazone; the weight of crude derivative showed that consistent yields of 90% of the dialdehyde could be expected. Since this solution was found satisfactory for these studies, the aldehyde was not isolated, thus avoiding loss of product. The bis-dinitrophenylhydrazone, after recrystallization from alcohol,[17b] melted at 278–280°.[17c]

Acetonedicarboxylic Acid.—This intermediate was prepared according to the directions of Adams and coworkers.[18]

Condensation Reactions.—The duplication of biological conditions *in vitro* demands that the reaction be carried out at high dilution. In view of the solubility of tropanone, it could be hardly expected that the product could be isolated in amounts sufficiently quantitative to indicate the extent of the condensation. Hence, either Schöpf's practice of precipitating the picrate,[4] or Robinson's procedure of preparing the dipiperonylidine derivative[1a] was employed; it was confirmed that either derivative was formed substantially quantitatively, thus facilitating a check on the yields of the condensation reaction.

After preliminary experiments, the following were adopted as the "standard" conditions for condensation, in comparison with which the effects of modifications and deviations were evaluated: Succinaldehyde solution prepared from 5.8 g. of dioxime as already described was made up to known exact volume and divided into two equal portions. One portion, containing 1.94 g. of aldehyde (0.0225 mole based on 90% conversion from the dioxime) was placed a 1-liter Erlenmeyer flask containing about 200 ml. of water; to it was added 5.84 g. (0.04 mole) of acetonedicarboxylic acid and 2.7 g. (0.04 mole) of methylamine hydrochloride. Using the Beckman *p*H meter, the *p*H of the solution was adjusted to the desired point by means of a saturated solution of disodium phosphate, and the volume made up to one liter. The solution was then allowed to stand at room temperature for three days, during which time appreciable effervescence of carbon dioxide was observed. An aliquot portion, usually a tenth, was used as already described to estimate the yield of tropanone; the remainder of the reaction mixture was combined with other residues similarly obtained for the isolation of free tropanone.

(7) Harries, *Ber.*, **41**, 674 (1908).

(8) Türk, *Ann.*, **343**, 361 (1905).

(9) Yourtee, Thesis, University of Maryland, 1943.

(10) Wohl and Schweitzer, *Ber.*, **39**, 890 (1906).

(11) Keimatsu and Yokata, *J. Pharm. Soc. Japan*, **542**, 284 (1927).

(12) Braun and Sobecki, *Ber.*, **44**, 2534 (1911).

(13) (a) Ciamician and Dennstedt, *ibid.*, **17**, 533 (1884); (b) Harries, *et al.*, *ibid.*, **34**, 1488 (1901); **35**, 1183 (1902); **39**, 3670 (1906); **41**, 255 (1908); (c) Willstätter and Heubner, *ibid.*, **40**, 3871 (1907); (d) Mannich and Budde, *Arch. Pharm.*, **270**, 283 (1932).

(14) *Cf.* "Beilstein," 4th ed., vol. 1, p. 767.

(15) Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

(16) (a) Wislicenus, *Ann.*, **192**, 106 (1878); (b) Freundler and Ledru, *Compt. rend.*, **140**, 795 (1905).

(17a) Eastman synthetic pyrrole offers no advantage over the practical grade. The use of hydroxylamine sulfate, which is appreciably cheaper than the hydrochloride, affects the yields adversely.

(17b) This compound showed unusual electrical properties. When freshly rubbed the dry yellow crystals would cling to glass and were difficult to place into a melting point tube. When spread on a piece of paper under which rubbed ebony was moved, the crystals acted as do iron filings under the influence of a magnet.

(17c) Mathieson and Hagedorn, *Mikrochemie. ver. Mikrochim. Acta*, **29**, 55 (1941); *C. A.*, **35**, 5923 (1941).

(18) Adams, Chiles and Rassweiler, "Organic Syntheses," Coll. Vol. I, p. 10.

For estimating the yield, the aliquot portion was saturated with potassium carbonate and repeatedly extracted with ether. The solvent was removed from the combined ethereal extracts and the residue concentrated to about 25 ml. This may be treated in either of two ways: (a) Add 1 g. of piperonal in 25 ml. of ethanol and 0.8 g. of potassium hydroxide in 5 ml. of water; reflux for fifteen minutes, when a reddish-brown precipitate forms that turns yellow; addition of water completes the deposition of the dipiperonylidene derivative, which may be collected on a tared filter, washed, dried and the yield of tropanone calculated. The derivative, recrystallized from ethyl acetate, melts at 214°.[18] (b) Add an ethereal solution of anhydrous picric acid, whereupon tropanone picrate separates quantitatively (thus permitting the calculation of yield). Tropanone picrate, recrystallized from water, melts 220°.[4]

In Table I are summarized the results of experiments showing the effect of *p*H on the condensation. It will be observed that they confirm substantially the observations of Schöpf and Lehmann.[4]

TABLE I

INFLUENCE OF *p*H ON YIELDS OF TROPANONE

*p*H of expt.		Yield, %	
Initial	Terminal	Obs.	Schöpf,[a]
5.0	5.1		54
5.2	5.7	58.1	
7.0	7.0		65
7.05	7.46	62.4	
11.0	10.7		64
11.02	9.85	60.3	

[a] The results of Table I suggest that if these condensations are to be adapted practically, the *p*H of the reaction need not be adjusted accurately.

It was found early that for 0.0225 mole succinaldehyde, the acetonedicarboxylic acid may be varied from 0.04 to 0.05 mole without affecting the yield of tropanone.

Since, under the "standard" conditions, the yields of tropanone, even if 100%, can never exceed 3.1 g., it would be desirable to operate with smaller volumes, that is, at higher concentrations. The results of experiments to this end are summarized in Table II.

TABLE II

EFFECT OF CONCENTRATION ON YIELD OF TROPANONE

0.0225 mole succinaldehyde; 0.04 mole acetonedicarboxylic acid; 0.04 mole methylamine hydrochloride

Volume, ml.	*p*H	Picrate, g.	Yield, %
1000	7.1	5.17	62.4
500	11.02	5.0	60.3
250	10.9	4.15	50.0[a]

[a] This value is low. Some product was inadvertently lost before precipitation as picrate. It is believed the actual yield would be very near that obtained at higher dilutions.

To test further the practicability of working with higher concentrations a reaction was carried out with the succinaldehyde from 23.2 g. (0.2 mole) of dioxime, 21.6 g. of methylamine hydrochloride (0.32 mole) and 46.7 g. (0.32 mole) of acetonedicarboxylic acid in a total volume of 2 liters. The condensate from two such reactions was extracted with ether, the extract dried over anhydrous sodium sulfate and distilled, the product coming over at 113° at 25 mm. pressure. The distillate, which crystallized, weighed 27.0 g. (0.194 mole). Assuming 90% conversion of the oxime into the aldehyde, the theoretical yield of tropanone would be 0.36 mole; on the basis of 60 to 65% yields of tropanone, as already indicated, 83 to 90% of the tropanone actually formed was isolated in pure form.

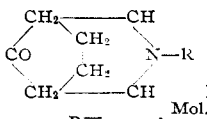
Reduction of Tropanone.—Willstätter reduced tropanone electrolytically and with zinc dust and hydriodic acid; his product was a mixture of tropanol and pseudo-tropanol.[19]

A twentieth mole, 6.95 g., of pure tropanone was dissolved in 150 ml. of commercial absolute ethanol and shaken in hydrogen at 10 atmospheres with 0.1 g. of platinum oxide. The calculated hydrogen was taken up in an hour. The catalyst was removed, the solvent taken off at reduced pressure, and the product distilled at 120–125° at 15 mm. pressure. The distillate crystallized, and weighed 6 g. That the product was pure tropanol was indicated by its picrate m. p. 275° (pseudo tropanol picrate melts at 258°[20]) and hydrochloride, of its benzoyl ester, which melted 267–268°.[21]

Homologs and Analogs of Tropanone.—Since Schöpf's modification of Robinson's original synthesis of tropanone appeared practicable, the reaction was further investigated to determine whether methylamine might be replaced by other primary amines. Accordingly, the "standard" conditions for condensation were repeated but with methylamine replaced by the following: (a) ethylamine; (b) isopropylamine; (c) benzylamine; (d) ethanolamine. The isopropylamine condensation product was isolated as the picrate; the other three were isolated as their dipiperonylidene derivatives. The experimental data are summarized in Table III.

TABLE III

N-HOMOLOGS AND ANALOGS OF TROPANONE



Dipiperonylidene derivative

R=	Mol. formula	M. p., °C.	Yield, %	Analyses for N, % Calcd.	Found	
—C_2H_5	$C_{25}H_{23}O_5N$	184–185	71.9	3.34	3.18	3.12
—$CH_2C_6H_5$	$C_{30}H_{25}O_5N$	194–195	30.0	2.89	2.89	2.85
—CH_2CH_2OH	$C_{25}H_{23}O_6N$	230–231	63.4	3.23	3.06	2.98
—$CH(CH_3)_2$[a]			51.6			

[a] Product isolated as the picrate and not analyzed. However, the behavior of the condensation reaction and the nature of the product encourage the belief that N-isopropyl-nor-tropanone was formed.

These results indicate that higher homologs and analogs of tropanone may be obtained, and no difficulty is anticipated in the reduction to the corresponding tropanol. The use of the tropanols and their pseudo-isomers in the further synthesis of compounds related to medicinally valuable substances requires no imagination. These will be studied in future investigations.

Summary

1. It has been shown that the philosophically intriguing hypothesis with respect to the formation of tropanone, in nature, demonstrated as probable by Schöpf, is amenable to practical application in the laboratory.

2. The condensation of succinaldehyde, acetonedicarboxylic acid and a primary amine will take place to form tropanone derivatives of interest to the medicinal chemist.

BALTIMORE, MD. RECEIVED APRIL 25, 1946

(19) Willstätter and Iglauer, *Ber.*, **33**, 1170 (1900).

(20) Willstätter, *ibid.*, **33**, 1173 (1900).

(21) Cliff and Tutin, *J. Chem. Soc.*, **95**, 1970 (1909).