sulfonyl chloride and 16.1 g. of (−)-2-(2-cyclopenten-1-yl)-ethanol, $[\alpha]^{32}\text{D}$ −72.3° (chf.), in 35 ml. of anhydrous ether; the mixture was stirred and kept at −15° throughout the addition. After one week in the refrigerator, the mixture was treated with cold dilute sulfuric acid, the ether layer separated, and the aqueous layer extracted twice with ether. The combined ether layers were washed with water, dried over sodium sulfate and stripped, yielding 39.1 g. of the desired (crude) tosyl ester as an oil $[\alpha]^{28.5}\text{D}$ −26.1° (*c* 5.1, chloroform). The ester was not purified further.

Anal. Calcd. for $C_{14}H_{18}O_3S$: S, 12.02. Found: S, 12.96.

A solution of 38.8 g. of the *p*-toluenesulfonate in 40 ml. of anhydrous ether was added dropwise to a solution of 5.8 g. of lithium aluminum hydride in 60 ml. of anhydrous ether. The addition required 45 minutes. The reaction mixture, worked up in the normal manner, yielded 2.1 g. (15%) of 3-ethylcyclopentene, b.p. 96–98° (760 mm.), n^{25}_{D} 1.4278, $[\alpha]^{24}\text{D}$ −69.9° (*c* 7.5, chloroform); lit.[40] (for racemic hydrocarbon) b.p. 96° (760 mm.), $n^{25}\text{D}$ 1.4300.

Anal. Calcd. for C_7H_{12}: C, 87.4; H, 12.58. Found: C, 86.9; H, 13.18.

Oxidation of (−)-3-Ethylcyclopentene.—Ozone was passed through a solution of 1.31 g. of (−)-3-ethylcyclopentene in 150 ml. of ethyl acetate, the mixture being immersed in a methanol–Dry Ice-bath throughout. After 30 minutes of passage at 5–6 bubbles per second, the reaction was complete, as evidenced by the oxidation of potassium iodide by the outflow of gases. The solution of ozonide was added, at the rate of three drops per second, to a well-stirred ice-cold mixture of 150 ml. of 5% sulfuric acid and 4 ml. of 30% hydrogen peroxide. The reaction mixture was concentrated on the steam-bath, made just alkaline with sodium carbonate, and evaporated to dryness. The dry salt mixture (39.8 g.) was treated with 50 ml. of water, acidified and extracted six times with ether. The combined ether solution was washed with 30% sodium chloride and dried. Distillation of the ether and acetic acid left 1.0 g. of a brown oil, which was treated with 10 ml. of water. Extraction with ether and evaporation of the extracts yielded 0.46 g. of α-ethylglutaric acid as a colorless viscous oil, $[\alpha]^{30}\text{D}$ +3.20° (*c* 6.25, ethanol), whose infrared spectrum was substantially identical with that of authentic α-ethylglutaric acid, resolved *via* the stychnine salt.[14] The spectra featured bands at 3.25 (shoulder), 3.40, 3.80 (shoulder), 5.85, 6.85, 7.05, 7.75–8.25, 8.50, 9.00, 9.30 (shoulder), 9.90 (shoulder), 10.75 and 11.70 (shoulder) μ. The acid was *ca.* 23% optically pure, based on $[\alpha]\text{D}$ (max.) 14.1° (ethanol).[14,41]

Oxidation of (+)-2-Cyclopentene-1-acetic Acid.—In a preliminary experiment racemic 2-cyclopentene-1-acetic acid (10 g.) in 150 ml. of anhydrous ethyl acetate was ozonized at −78°, and the solution of the ozonide added dropwise, over a period of 25 minutes, to an ice-cold well-stirred mixture of 20 ml. of 30% hydrogen peroxide and 150 ml. of 5% sulfuric acid. The solution was concentrated to about one-quarter the original volume and treated with 7.3 g. of calcium oxide. The filtrate from the resulting calcium sulfate was evaporated to 20 ml.; on standing in the refrigerator overnight, the solution deposited 2.0 g. of crystals. The crystals were filtered, treated with 8 ml. of acetone and the resulting suspension filtered from remaining calcium sulfate. The acetone filtrate, on concentration to 3 ml. and cooling, deposited 0.48 g. of needle rosettes, m.p. 117–118° (lit.[42] m.p. 116–118° for 3-carboxyadipic acid).

In precisely the same manner, 2.5 g. of 2-cyclopentene-1-acetic acid, $[\alpha]^{28}\text{D}$ +106.9° (*c* 5.4, chloroform), obtained *via* the brucine salt, was oxidized to give 0.6 g. of 3-carboxyadipic acid, m.p. 92–104°, $[\alpha]^{31}\text{D}$ −12.75° (*c* 5.2, acetone) (lit.[17] m.p. 102–103°, $[\alpha]^{20}\text{D}$ +27.2° (acetone)[43]).

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[40] H. Adkins and A. K. Roebuck, THIS JOURNAL, **70**, 4041 (1948).

[41] Since the starting acid was 59% optically pure, and since racemization could not have taken place in any but the last step, the oxidation therefore entailed about 60% racemization.

[42] F. W. Kay and W. H. Perkin, Jr., *J. Chem. Soc.*, 1640 (1906).

[43] The starting acid, 98% optically pure, therefore yielded 3-carboxyadipic acid of only 47% optical purity, a fact reflected in the melting point range of the sample. The oxidation consequently entailed 52% racemization; *cf.* also ref. 41. It is interesting that the optical instability of 3-carboxyadipic acid and/or its esters has been noted in a similar connection (K. Freudenberg, H. Meisenheimer, J. T. Lane and E. Plankenhorn, *Ann.*, **543**, 162 (1940); ref. 17).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Utilization of Alkyl 2-Cyclohexylethyl Ketones in the Pfitzinger Reaction[1]

BY CHARLES G. SKINNER AND HENRY R. HENZE

RECEIVED JANUARY 24, 1955

The study of the behavior in the Pfitzinger reaction of mixed ketones, containing two methylene groups adjacent to the carbonyl function, has been extended to a series of cyclohexane alkanones, $C_6H_{11}CH_2CH_2CO{-}R$. Except for the first member of the series, only the α-methylene group of the unsubstituted alkyl of these ketones was found to participate in this reaction.

The condensation of an alkali metal salt of isatic acid with ketones, possessing at least one α-methylene group, to form substituted cinchoninic acids is termed the Pfitzinger reaction.[2] The original techniques have been extended by many workers, and reviews are available which contain critical discussions of the practical and theoretical implications.[3]

Buu-Hoï and Cagniant[4] in their attempts to prepare a series of substituted cinchoninic acids from the alkyl phenyl ketones, $C_6H_5CO(CH_2)_nCH_3$, observed that of the latter only those for which *n* is equal to or less than 2 condense in the usual fashion with isatin. Subsequently, however, valerophenone[5] and caprophenone[6] have been found to give the expected substituted cinchoninic acid on prolonged heating.

In order to study the possibility of steric hindrance in this condensation, a new series of ketones, alkyl 2-cyclohexylethyl ketones, was prepared and studied utilizing the "normal" Pfitzinger conditions. The ketones prepared are summarized in Table I. Since we were able to isolate solid semi-

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[1] From the Ph.D. thesis of Charles G. Skinner, June, 1953.

[2] W. Pfitzinger, *J. prakt. Chem.*, [2] **33**, 100 (1888); **38**, 583 (1888); **56**, 283 (1897); **66**, 263 (1902).

[3] (a) W. C. Sumpter, *Chem. Revs.*, **34**, 393 (1949); (b) R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 222–229; (c) Vol. IV, pp. 47–56, pp. 215–225.

[4] Ng. Buu-Hoï and P. Cagniant, *Bull. soc. chim.*, 123 (1946).

[5] L. K. Yourtee, Ph.D. dissertation, University of Texas, June, 1948.

[6] (a) Unpublished results (1949) by H. R. Henze and R. E. Leslie, University of Texas; (b) G. P. Mueller and R. E. Stobaugh, THIS JOURNAL, **72**, 1598 (1950).

TABLE I

ALKYL 2-CYCLOHEXYLETHYL KETONES, $C_6H_{11}CH_2CH_2CO—R$

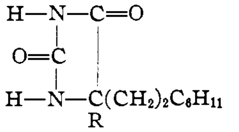
R	B.p., °C.	Mm.	Yield, %	n^{20}_D	d^{20}_4	MR Calcd.	MR Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Semicarbazone m.p., °C.
CH_3	86–89	7	44	1.4576	0.9161	46.19	46.42	77.87	77.81	11.76	11.90	171[a]
C_2H_5	95–98	3	80	1.4552	.8992	50.81	50.79	78.51	78.13	11.98	12.04	169–170[b]
n-C_3H_7	98–100	2	80	1.4573	.8947	55.43	55.52	79.06	79.02	12.16	12.25	125–127[c]
i-C_3H_7	98–101	6	52	1.4538	.8955	55.43	55.12	79.06	78.84	12.16	12.01	126–127[d]
n-C_4H_9	102–104	2	80	1.4581	.8915	60.04	60.09	79.53	79.20	12.32	12.46	......
n-C_5H_{11}	107–109	4	85	1.4588	.8899	64.66	64.59	79.93	79.85	12.46	12.51	......
i-C_5H_{11}	129–130	5	85	1.4578	.8860	64.66	64.76	79.93	79.85	12.46	12.35	......

Anal. [a] Calcd. for $C_{11}H_{21}N_3O$: N, 19.89. Found: N, 19.77. [b] Calcd. for $C_{12}H_{23}N_3O$: N, 18.65. Found: N, 19.00. [c] Calcd. for $C_{13}H_{25}N_3O$: N, 17.56. Found: N, 17.67. [d] Calcd. for $C_{13}H_{25}N_3O$: N, 17.56. Found: N, 17.61.

carbazone derivatives from only the first three members of this series, in order properly to characterize these ketones, an attempt was made to prepare the corresponding hydantoins. The latter were obtained readily in good yield and are presented in Table II.

TABLE II

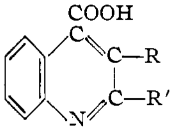
5-ALKYL-5-(2-CYCLOHEXYLETHYL)-HYDANTOINS



R	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	196.0–196.5	54	12.49	12.51
C_2H_5	214.5–215.5	70	11.76	11.81
n-C_3H_7	185.5–186.0	89	11.10	11.23
i-C_3H_7	218.0–219.0	67	11.10	11.34
n-C_4H_9	181.0–182.0	85	10.52	10.68
n-C_5H_{11}	206.0–206.5	75	9.99	10.30
i-C_5H_{11}	232.0	76	9.99	10.05

TABLE III

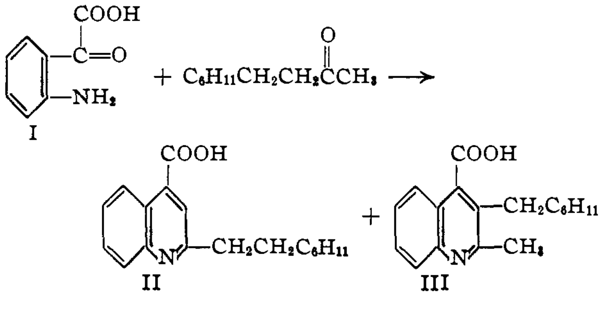
SUBSTITUTED CINCHONINIC ACIDS

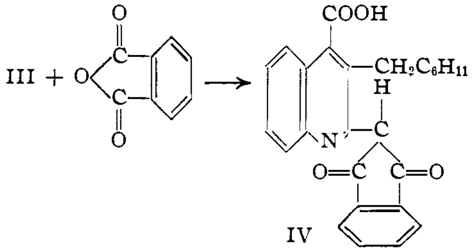


R	R′	M.p., °C. (dec.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
H	$CH_2CH_2C_6H_{11}$	168–169	48	76.29	75.58	7.47	7.56	4.94	5.16	283.4	284.8
$CH_2C_6H_{11}$	CH_3	289–291	8	76.29	75.21	7.47	7.46	4.94	5.06	283.4	284.0
CH_3[a]	$CH_2CH_2C_6H_{11}$	252–254	47	76.73	76.41	7.78	8.03	4.71	4.94	297.4	310.0
C_2H_5	$CH_2CH_2C_6H_{11}$	147–149	43	77.13	76.80	8.09	8.06	4.50	4.65	311.4	316.0
n-C_3H_7	$CH_2CH_2C_6H_{11}$	215–218	42	77.49	77.30	8.36	8.24	4.30	4.47	325.4	332.0
n-C_4H_9	$CH_2CH_2C_6H_{11}$	192–203	35	77.84	77.20	8.61	8.38	4.13	4.31	339.5	343.6
$CH_2CH(CH_3)_2$	$CH_2CH_2C_6H_{11}$	162–165	25	77.84	77.65	8.61	8.95	4.13	4.07	339.5	339.0

[a] Decarboxylation of this compound yielded the corresponding substituted quinoline which was isolated as a picrate, m.p. 178.5–180.0°. *Anal.* Calcd. for $C_{18}H_{23}N \cdot C_6H_3N_3O_7$: N, 11.62. Found: N, 11.62. Decomposition of the picrate produced the pure compound, m.p. 52–53°. *Anal.* Calcd. for $C_{18}H_{23}N$: N, 5.53. Found: N, 5.78.

In contrast to the acetophenone series studied by Buu-Hoï and Cagniant,[4] the alkyl 2-cyclohexylethyl ketones, which contain the $-CH_2COCH_2-$ grouping, may exhibit two active methylene groups and thus possibly produce two isomers; however, we were able to isolate isomers only in the reaction product of 4-cyclohexyl-2-butanone. These isomers were separated by initial recrystallization of the reaction mixture from glacial acetic acid followed by treatment with dioxane, and the structure assigned to each is based on the fact that only the higher melting isomer formed a phthalone derivative because of the presence of an active methyl group.[7]





The monosubstituted isomer was formed preferentially in approximately a 6-to-1 ratio. In view of this isomer ratio, and the fact that no product could be isolated from the attempted condensation of 1-cyclohexyl-4-methyl-3-pentanone with isatin, it was concluded that the "major" reaction product in this series of ketones is a 3-alkyl-2-(2-cyclohexylethyl)-cinchoninic acid. These data are summarized in Table III.

The yields of the substituted cinchoninic acids formed from the n-alkyl 2-cyclohexylethyl ketones vary from 48 to 35%; 2-cyclohexylethyl methyl

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[7] R. C. Elderfield, "Heterocyclic Compounds," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 81.

ketone produced the higher figure and 2-cyclohexylethyl amyl ketone gave the lower. These moderately low yields may be accounted for by the decomposition of both the ketone and isatin[8] during the prolonged heating period required. Samples of both isatin and 2-cyclohexylethyl *n*-amyl ketone, respectively, were treated with hot alkali in the usual Pfitzinger procedure, and there was recovered only 45% of the isatin and 61% of the ketone. These results indicate that in this series of ketones, $C_6H_{11}CH_2CH_2CO(CH_2)_nCH_3$, a substituted cinchoninic acid is obtained up to *n* equal 4. Even though no study was made of higher homologs, the yields of the *n*-amyl and isoamyl derivatives indicate that the condensation with higher homologs probably would occur, although in progressively smaller degree of conversion.

The ultraviolet spectra of all these substituted 4-quinolinecarboxylic acids presented a very high degree of similarity. When all seven spectra were plotted on a single graph paper the curves so developed that one could not distinguish one from another, with the exception of the single monosubstituted cinchoninic acid prepared. The region of maximum absorption was about 315 mμ and that of minimum absorption about 260 mμ. These data are in good agreement with the ultraviolet absorption spectra for the simple substituted cinchoninic acids prepared by Henze and Carroll.[9] All ten of the 2- and 2,3-alkylsubstituted cinchoninic acids prepared by them possessed maximum ultraviolet absorption between 314 and 319 mμ, and minimum absorption between 258 and 264 mμ.

Experimental

Preparation of Cyclohexanepropionyl Chloride.—One equivalent of cyclohexanepropionic acid was added to a gently refluxing solution of 3 equivalents of thionyl chloride; after refluxing an additional hour, the excess thionyl chloride was removed under reduced pressure. The acid chloride was recovered in from 90 to 95% yield by distillation under reduced pressure, b.p. 78–81° (2 mm.). Treatment of this compound with ammonium hydroxide yielded the amide,[10] m.p. 120–121°.

Preparation of Alkyl (2-Cyclohexylethyl) Ketones.—All of these ketones were prepared by the same general procedure[11] with the exception of the methyl and isopropyl derivatives, the significant difference being that in these latter cases the reaction was carried out wholly in ether as the solvent. The physical characteristics and analytical data for these ketones are presented in Table I. A detailed description of 1-cyclohexane-2-pentanone is presented as being typical.

A Grignard reagent was prepared in the usual fashion using 10.8 g. (0.44 g.-atom) of magnesium, 54.0 g. (0.50 mole) of ethyl bromide and a total of 500 ml. of dry ether, and was treated with 46.0 g. (0.25 mole) of anhydrous cadmium chloride added in three equal portions. The ether was distilled rapidly with constant stirring of the reaction mixture. After addition of 100 ml. of dry benzene to the semi-solid residue, the mixture was again distilled to dryness. Another 100-ml. portion of benzene was added and the solid broken up by stirring. To this mixture was added 17.5 g. (0.10 mole) of cyclohexanepropionyl chloride, with constant stirring, at such a rate that refluxing was not too rapid. After warming to reflux for one hour, the flask was placed in an ice-bath and the adduct decomposed with an ice–6 *N* hydrochloric acid mixture. The benzene phase was decanted, dried over calcium sulfate, and the solvent removed. The ketone then was distilled under reduced pressure to yield 14.6 g. (80% yield) of product.

Preparation of 5-Alkyl-5-(2-cyclohexylethyl)-hydantoins.—Since all of the hydantoins were prepared by the same general procedure,[12] a detailed description of the preparation of only 5-(2-cyclohexylethyl)-5-ethylhydantoin will be presented here. The properties of these substituted hydantoins are summarized in Table II.

To a mixture of 1.7 g. (0.03 mole) of potassium cyanide and 7.2 g. (0.13 mole) of ammonium carbonate was added 20 ml. of an alcohol–water solution of 3.6 g. (0.02 mole) of 1-cyclohexane-2-pentanone. The reaction mixture then was placed in a glass liner within a steel bomb and heated at 110° for approximately 8 hours. After cooling, the solution was acidified with concentrated hydrochloric acid and evaporated to dryness on a steam-cone under a hood. The solid residue then was dissolved in 10% sodium hydroxide solution, and this solution extracted with ether to remove any non-acidic organic material. The basic aqueous phase was acidified with dilute hydrochloric acid and a white crystalline solid precipitated immediately. The material was recrystallized from alcohol–water and dried at 110° to yield 4.0 g. (70% yield).

Interaction of 4-Cyclohexyl-2-butanone with Isatin (II and III).—There was charged 22.5 g. (0.15 mole) of 4-cyclohexane-2-butane, 14.7 g. (0.10 mole) of isatin and 175 ml. of a 13% solution (0.40 mole) of potassium hydroxide in 88% ethanol–water. The mixture was stirred under reflux on a steam-cone for 50 hours, following which the alcohol was removed and the solid taken up in water. The alkaline solution was extracted with ether to remove unreacted ketone, and then was treated with portions of 50% acetic acid until acidic. Several fractions were obtained by recovering the precipitate at various *p*H values. The initial precipitate (*p*H 8.9) was mostly silica, followed by a bulky precipitate at *p*H 7.5 which contained the major portion of the reaction product. Below *p*H 6.5 there was recovered unreacted isatin. The material isolated at *p*H 7.5 was taken up in glacial acetic acid and there was recovered on cooling and recrystallization from dioxane the lower melting isomer, m.p. 168–169° dec. The filtrate from glacial acetic acid then was evaporated to a small volume, diluted with water, and the precipitate macerated in boiling dioxane. The soluble portion yielded the lower melting product and the insoluble portion proved to be the isomeric higher melting form, m.p. 285–290° dec. These isomeric substituted-cinchoninic acids were distinguished by their melting points and X-ray diffraction patterns. There was recovered 13.55 g. (47.8% yield) of the lower melting form, 2.18 g. (7.7% yield) of the higher melting form, 2.4 g. of unreacted ketone and a total of 2.5 g. of isatin from various recrystallizations. This is a total accountability of 72.5% of the reactants. The isomer ratio is approximately 6.2 to 1 with the lower melting form in excess.

Anal. of higher melting form. Calcd. for $C_{18}H_{21}NO_2$: neut. equiv., 283.4; C, 76.29; H, 7.47; N, 4.94. Found: neut. equiv., 284.0; C,[13] 75.21; H, 7.46; N, 5.06. Found (lower melting form): neut. equiv., 284.8; C, 75.85; H, 8.13; N, 5.16.

The structural formulas of these compounds indicate that only III possesses an active methyl group, thus an attempt was made to prepare a phthalone derivative[14] to determine which of the two isomeric products contained an active methyl group.[7]

Phthalone Derivative IV of Higher Melting Form III.—An intimate mixture of 0.4 g. of substituted cinchoninic acid (higher melting form) produced in the preceding synthesis and 1.4 g. of phthalic anhydride was heated in an oil-bath at 240–250° for 20 minutes. After cooling, the

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[8] A. F. Isbell and H. R. Henze, THIS JOURNAL, **66**, 2096 (1944), reported that isatin is decarbonylated to anthranilic acid under the usual Pfitzinger conditions.

[9] H. R. Henze and D. W. Carroll, *ibid.*, **76**, 4580 (1954).

[10] N. Zelinsky, *Ber.*, **41**, 2677 (1908), reported a m.p. of 120–123°.

[11] Patterned after the methods of J. Cason, THIS JOURNAL, **68**, 2078 (1946).

[12] Patterned after the method of H. R. Henze and L. M. Long, *ibid.*, **63**, 1951 (1941), using ethyl alcohol–water as a solvent instead of acetamide.

[13] Repeated analysis of some of the substituted cinchoninic acids produced in this investigation yielded low carbon values. The compounds burned with difficulty to a tar even in an open flame.

[14] Patterned after the procedure of M. T. Bogert and M. Heidelberger, THIS JOURNAL, **34**, 183 (1912).

solid was taken up in glacial acetic acid, and the solution poured over flaked ice. There was recovered 0.5 g. (91% yield) of yellow material, m.p. (out of alcohol–water) 320°.

Anal. Calcd. for $C_{26}H_{23}NO_4$: C, 75.58; H, 5.61; N, 3.39. Found: C, 75.62; H, 5.82; N, 3.62.

Attempted Preparation of Phthalone of Lower Melting Form II.—An intimate mixture of 2.3 g. of the isomeric substituted cinchoninic (lower melting form) produced in the preceding synthesis and 1.2 g. of phthalic anhydride was heated in an oil-bath for 3 hours. On working up as above there was recovered 1.72 g. of unreacted starting material (75% recovery). There was undoubtedly some decarboxylation of the acid to the corresponding substituted quinoline during the reaction period.

Preparation of 3-Alkyl-2-(2-cyclohexylethyl)-cinchoninic Acids.—The general procedure for the preparation of all substituted cinchoninic acids formed in this investigation was essentially the same. Only one compound was isolated in each of the other condensations even though a search was made for isomeric products. Thus, the condensation of 1-cyclohexyl-3-pentanone with isatin will be presented in detail as a sample preparation of the substituted cinchoninic acids formed which are summarized in Table III.

A mixture of 10.3 g. (0.06 mole) of 1-cyclohexyl-3-pentanone and 12.5 g. (0.08 mole) of isatin was dissolved in 36 ml. of 85% alcohol–water containing 31% by weight (0.12 mole) of potassium hydroxide. The solution then was heated on a steam-cone for 12 hours, cooled, diluted with 200 ml. of water and extracted with ether to remove unreacted ketone. After careful acidification with 50% acetic acid to *p*H 7.5 there was an immediate precipitation of gray micro-crystals. After sitting overnight in the refrigerator the solid was recovered and recrystallized from alcohol–water. There was obtained 9.0 g. (47% yield) of the substituted cinchoninic acid.

Frequently it was found desirable to remove excess water by centrifugation before filtering after the acidification step.

Attempted Condensation of 1-Cyclohexyl-4-methyl-3-pentanone with Isatin.—This particular condensation is unique, among those studied, in that in the ketone here utilized there is only one methylene group *alpha* to the carbonyl of the ketone. Therefore, only one cinchoninic acid is possible from the normal Pfitzinger condensation.

No substituted cinchoninic acid was obtained from any of the several experiments tried; usually the ketone was recovered in about 40% accountability as compared to a 60% accountability under comparable conditions using no isatin in the reaction mixture. In this connection, it is of definite interest to note that Mead and co-workers[15] attempted the condensation of isopropyl methyl ketone and isatin under the usual Pfitzinger conditions, but the anticipated 2-(1-methylethyl)-cinchoninic acid was not obtained.

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[15] J. F. Mead, A. E. Senear and J. B. Koepfli, THIS JOURNAL, **68**, 2709 (1946).

AUSTIN, TEXAS

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE FORMER PHOSPHATE DIVISION, MONSANTO CHEMICAL CO.]

Carbamoylphosphonates[1]

BY THEODOR REETZ,[2] D. H. CHADWICK,[2] E. E. HARDY AND S. KAUFMAN[2]

RECEIVED FEBRUARY 3, 1955

The carbamoylphosphonates, $RR'NCOPO(OR'')_2$, may be prepared through the Arbusov reaction, the Michaelis reaction, amidation of methyl dialkoxyphosphinylformate or reaction of dialkyl phosphite with an isocyanate. Of these preparative methods, that of Arbusov is the most practical and generally applicable.

The preparation and properties of the carbamoylphosphonates as a new[3] class of compounds was of interest because of the possibility of preparing them by the direct reaction of a dialkyl phosphite and an isocyanate. It is known that dialkyl phosphites will add to the carbonyl group[4] and to carbon–nitrogen double bonds,[5] and sodium bisulfite has been reported to add to isocyanates producing carbamoylsulfonates.[6] It therefore seemed probable that dialkyl phosphites would react with isocyanates to produce carbamoylphosphonates.

$$RNCO + HPO(OR')_2 \longrightarrow RNHCOPO(OR')_2$$

The only report[3] of a compound of this class is that of the parent diethyl carbamoylphosphonate, $H_2NCOPO(OC_2H_5)_2$, prepared by allowing a solution of ethyl diethoxyphosphinylformate and anhydrous ammonia in alcohol to stand for several weeks.[7]

Initial attempts to effect reaction between dialkyl phosphites and isocyanates, made at relatively low temperature to avoid possible reversion of the expected products to the starting materials, were not successful. Therefore, before pursuing this approach further, we turned to more general methods for the preparation of phosphonates.

The Arbusov reaction was found to be generally applicable for the preparation of diethyl alkyl- and dialkylcarbamoylphosphonates from the corresponding alkyl- and dialkylcarbamoyl chlorides

$$RR'NCOCl + (C_2H_5O)_3P \longrightarrow RR'NCOPO(OC_2H_5)_2 + C_2H_5Cl$$
$$R = \text{alkyl},\ R' = \text{alkyl or hydrogen}$$

The monoalkylcarbamoyl chlorides were prepared by passing the theoretical amount of anhydrous hydrogen chloride into the isocyanates, and they were used without further treatment.

The Michaelis reaction also was found to be applicable, as applied to the preparation of diethyl dimethylcarbamoylphosphonate

$$(CH_3)_2NCOCl + NaPO(OC_2H_5)_2 \longrightarrow (CH_3)_2NCOPO(OC_2H_5)_2$$

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[1] Presented before the Division of Organic Chemistry at the 124th National Meeting of the American Chemical Society, Chicago, Ill., September, 1953.

[2] Organic Chemicals Div., Monsanto Chemical Co., St. Louis 4, Mo.

[3] Since this work was completed, it has come to our attention that B. A. Arbusov and N. I. Rizpolozhensky have reported the preparation of dialkyl diethylcarbamoylphosphonates: *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 847 (1952); *C. A.*, **47**, 10457 (1953). Their work and ours are complementary in that they varied the alkyl groups of the phosphonate esters, whereas we studied the preparation of a series of diethyl mono- and dialkylcarbamoylphosphonates by several synthetic routes.

[4] E. K. Fields, U. S. Patent 2,579,810 (1951); A. L. Morrison and F. R. Atherton, British Patent 682,706 (1952); A. N. Pudovik, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **22**, 462, 467, 473 (1952); V. S. Abramov, *ibid.*, **22**, 647 (1952); A. R. Stiles, U. S. Patent 2,593,213 (1952).

[5] E. K. Fields, THIS JOURNAL, **74**, 1528 (1952); A. N. Pudovik, *Doklady Akad. Nauk S.S.S.R.*, **83**, 865 (1952).

[6] S. Petersen, *Ann.*, **562**, 205 (1949).

[7] P. Nylen, *Ber.*, **57**, 1023 (1924).