and Mr. N. Coleburn for the use of their facilities and for their help.

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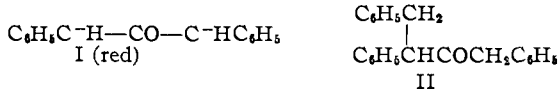
RECEIVED OCTOBER 8, 1957

DICARBANIONS OF DIBENZYL KETONE, DIBENZYL SULFONE AND α,β,β-TRIPHENYLPROPIONITRILE

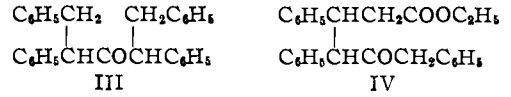
Sir:

We have observed that dibenzyl ketone is converted by two equivalents of potassium amide in liquid ammonia to a dark red dicarbanion I, the basic and nucleophilic strength of which is evidently much greater than that of the common colorless monocarbanion of this ketone. Thus, whereas the monocarbanion produced a mixture of products with benzyl chloride, the dicarbanion I reacted rapidly with a molecular equivalent of this halide to form, after acidification, a high yield of the monoalkylation product II, m.p. 72–73.5° (lit. m.p. 74–74.5°).[1]



I (red) II

Dicarbanion I gave with two molecular equivalents of benzyl chloride a good yield of dialkylation product III (apparently one diastereoisomer), m.p. 120.5–122° (lit. m.p. 121°),[2] *Anal.* Calcd. for $C_{29}H_{26}O$: C, 89.19; H, 6.71. Found: C, 89.07; H, 6.42.

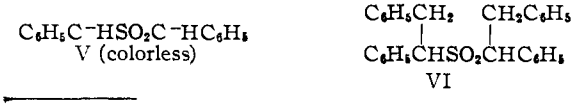


III IV

Although the monocarbanion of dibenzyl ketone failed to react appreciably with ethyl cinnamate in liquid ammonia during 0.5 hour, dicarbanion I rapidly underwent conjugate addition with a molecular equivalent of this α,β-unsaturated ester to form, after acidification, an excellent yield of ketone-ester IV (apparently a mixture of *threo* and *erythro* isomers). A recrystallized sample (m.p. 149–149.5°) was analyzed. *Anal.* Calcd. for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.65; H, 6.71.

Saponification of IV gave a good yield of the corresponding acid, m.p. 231.5–233.5° (apparently a single isomer). *Anal.* Calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.55; H, 5.87.

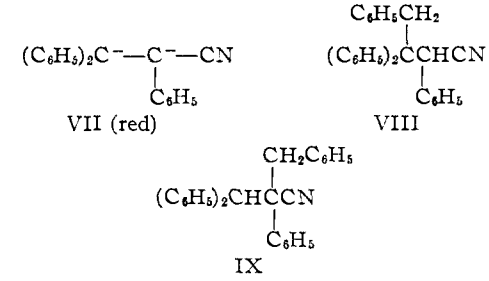
Similarly dibenzyl sulfone was converted by two equivalents of potassium amide in liquid ammonia to dicarbanion V (colorless) which reacted with two molecular equivalents of benzyl chloride to form a good yield of the dialkylation product VI, m.p. 187.5–188.5° (apparently one diastereoisomer). *Anal.* Calcd. for $C_{28}H_{26}SO_2$: C, 78.85; H, 6.14; S, 7.50. Found: C, 79.07; H, 5.97; S, 7.61.



V (colorless) VI

(1) A. McKenzie and R. Roger, *J. Chem. Soc.*, 571 (1927).
(2) C. Rattner, *Ber.*, **21**, 1316 (1888).

Also, α,β,β-triphenylpropionitrile was converted by two equivalents of potassium amide in liquid ammonia to a dark red dicarbanion VII, which apparently reacted preferentially at the β-position with a molecular equivalent of benzyl chloride to form, after acidification, a high yield of the monoalkylation product VIII, m.p. 125.5–128.5°. *Anal.* Calcd. for $C_{28}H_{23}N$: C, 90.04; H, 6.21; N, 3.75. Found: C, 90.02; H, 6.25; N, 3.81.



VII (red) VIII

IX

The common type of monobenzylation of α,β,β-triphenylproprionitrile at the α-carbon atom was effected by means of an equivalent of potassium amide to form IX, m.p. 185.5–187° which is isomeric with VIII. *Anal.* Calcd. for $C_{28}H_{23}N$: C, 90.04; H, 6.21; N, 3.75. Found: C, 90.14; H, 6.33; N, 3.88.

Studies on related condensations of multiple carbanions are in progress.

(3) National Science Foundation Predoctoral Fellow 1956–1958.

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RECEIVED NOVEMBER 11, 1957

γ-(3-PYRIDYL)-γ-METHYLAMINOBUTYRIC ACID AS A URINARY METABOLITE OF NICOTINE[1]

Sir:

Studies in the rat[2] and dog[3] with uniformly labelled-C^{14} (−)-nicotine have shown that virtually all of the administered radioactivity is excreted in the urine. In the dog, approximately 10% of the excretion was unchanged nicotine with the remainder distributed[4] between seven chromatographically distinct fractions.

We wish to report the first chemical identification of a compound obtained from the metabolism of nicotine in the intact animal.

A sample of 18-hour pooled urine from six dogs which had received nicotine (10 mg./kg. intravenously) portionwise under pentobarbital anesthesia during an 8-hour period was adjusted to *p*H 2 with 5 *N* HCl. The solution was placed on Dowex 50 × 4 (H+ form). After a water wash, material giving a positive Koenig reaction was eluted with 1 *N* ammonia water. The aqueous solution of the residue from the vacuum concentration of this fraction was extracted with chloroform and then at *p*H 10–11 placed on Dowex 1

(1) Appreciation is expressed for support of this work by the Tobacco Industry Research Committee and The American Tobacco Company.
(2) A. Ganz, F. E. Kelsey and E. M. K. Geiling, *J. Pharmacol. Exp. Therap.*, **103**, 209 (1951).
(3) D. R. Bennett, R. E. Tedeschi and P. S. Larson, *Arch. int. pharmacodyn.*, **98**, 221 (1954).
(4) F. B. Owen, Jr., and P. S. Larson, *ibid.*, in press.

(OH^- form). Following a water wash the column was eluted with 1 *N* acetic acid to give 383 mg. of brown solid which yielded a single Koenig positive spot (R_f 0.15) upon paper chromatography with 0.5 *N* ammonia water (1 vol.)–95% ethanol (1 vol.)–*n*-butanol (4 vol.). The spot corresponds to that obtained with authentic γ-(3-pyridyl)-γ-methylaminobutyric acid.[5] The brown solid was heated to 155° under nitrogen to give 43 mg. of clear chloroform-soluble oil, $\lambda_{max.}$ 262 mμ. The optical density of the oil in methanol corresponded to that calculated for 48 mg. of cotinine (5-(3′-pyridyl)-1-methylpyrrolidone-2). Paper chromatography in the aforementioned system and also in *sec*-butyl alcohol (45 vol.)–formic acid (8.4 vol.)–water (6.6 vol.) gave major Koenig positive spots corresponding to those of authentic cotinine. The oil yielded a yellow picrate with m.p. 104–106° corresponding to that of authentic continine picrate. The mixed melting point showed no depression.

Anal. Calcd. for $C_{16}H_{15}N_5O_8$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.49; H, 3.80; N, 17.19. The infrared spectra of authentic and isolated picrates in Nujol mulls were identical.[6] γ-(3-Pyridyl)-γ-methylaminobutyric acid (based on the amount of the lactam cotinine) accounts for approximately 5% of the administered nicotine.

It has been observed[7,8] that the urine of dogs following the administration of nicotine contains a substance insoluble in ether, which gives directly a red color with cyanogen bromide. Since γ-(3-pyridyl)-γ-methylaminobutyric acid gives this color reaction[4] and is insoluble in ether, the isolation of this acid from urine explains, in part at least, the appearance of the color. Control dog urine yields neither the color reaction nor the methylamino acid.

Thermal cyclization of γ-(3-pyridyl)-γ-methylaminobutyric acid from urine resulted in the formation of cotinine with $[\alpha]^{30}_{5461}$ −18.77° in methanol. A sample of γ-(3-pyridyl)-γ-methylaminobutyric acid prepared *in vitro* from (−)-nicotine[5] was cyclized under similar conditions to give cotinine with $[\alpha]^{21.5}_{5461}$ −18.16°. These two rotations are of the same sign and order of magnitude as that of cotinine prepared from (−)-nicotine by the method of Pinner.[5] It is inferred, therefore, that in the metabolic processes leading to the formation of γ-(3-pyridyl)-γ-methylaminobutyric acid the optical configuration of the asymmetric carbon atom of (−)-nicotine is retained.

The urine of dogs receiving (−)-nicotine contains cotinine in addition to γ-(3-pyridyl)-γ-methylaminobutyric acid and other metabolites, as demonstrated by paper chromatography and chloroform extraction. Studies *in vitro* with γ-(3-pyridyl)-γ-methylaminobutyric acid showed that aqueous solutions at *p*H 7 and below spontaneously yield cotinine at room temperature. In fresh samples of urine, voided usually in the region of *p*H 6, the γ-(3-pyridyl)-γ-methylaminobutyric acid fraction was greater than in older samples in which the cotinine fraction had become larger. Consequently, cotinine in the urine of dogs may be entirely an artifact which arose from the spontaneous lactamization. An attractive alternate explanation for the appearance of the lactam is the possibility that, in the metabolism of nicotine, cotinine is an intermediate which can in subsequent enzymatic reactions be hydrolyzed to γ-(3-pyridyl)-γ-methylaminobutyric acid.

(5) H. McKennis, Jr., L. B. Turnbull, H. N. Wingfield, Jr., and L. J. Dewey, THIS JOURNAL, in press.

(6) Kindly obtained by Mr. W. B. Wartman, Jr., The American Tobacco Company Research Laboratory.

(7) P. S. Larson and H. B. Haag, *J. Pharmacol. Exp. Therap.*, **76**, 240 (1942).

(8) P. S. Larson, H. B. Haag and J. K. Finnegan, *ibid.*, **86**, 239 (1946).

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RECEIVED OCTOBER 10, 1957

METHYL AFFINITIES OF DIENES

Sir:

A comparatively simple technique, developed in our laboratories some years ago and described in previous communications,[1-3] permits us to measure

TABLE I

Compound	*T*, °C.	k_2/k_1	No. of exp.	Range of mole % of the investigated comp.
Cumulated dienes				
Allene	54.8	20.3 ± 0.2	3	3.4–6.3
Allene	64.9	17.6 ± 0.2	3	3.4–6.3
Allene	75.0	16.0 ± 0.2	3	3.4–6.3
Allene	85.1	14.3 ± 0.2	3	3.4–6.3
Butadiene-1,2	54.8	17.2 ± 1.0	4	2.2–8.8
Butadiene-1,2	64.9	14.8 ± 2.0	5	2.9–7.4
Butadiene-1,2	75.0	13.4 ± 1.0	5	2.0–9.2
Butadiene-1,2	85.1	13.5 ± 1.0	6	2.2–6.5
Conjugated Dienes				
Butadiene-1,3	54.8	2350 ± 35	4	0.06–0.15
Butadiene-1,3	64.9	2015 ± 30	3	.06– .15
Butadiene-1,3	75.0	1790 ± 40	3	.07– .12
Butadiene-1,3	85.1	1630 ± 10	3	.07– .14
Isoprene	54.8	2460 ± 70	3	0.08–0.16
Isoprene	64.9	2090 ± 50	4	.08– .16
Isoprene	75.0	1800 ± 30	4	.04– .16
Isoprene	85.1	1470 ± 30	3	.04– .16
2,3-Dimethyl-butadiene-1,3	64.9	2230 ± 70	4	0.07–0.21
1,4-Diphenyl-butadiene-1,3	64.9	378 ± 6	3	0.06–0.13
2,5-Dimethyl-hexadiene-2,4	64.9	21.3[a]	7	0.2–7.0
1,1,4,4-Tetra-phenyl buta-diene-1,3	64.9	~60[b]		
Isolated Dienes				
Hexadiene-1,5	64.9	68[a]	9	1.0–7.7
2,5-Dimethyl-hexadiene-1,5	64.9	77[a]	6	1.0–6.5

[a] k_2/k_1 determined by the extrapolation to zero monomer concentration, using the procedure described by Buckley, Leavitt and Szwarc, THIS JOURNAL, **78**, 5557 (1956). [b] This compound was investigated in toluene since it is insoluble in isoöctane. The results were recalculated for isoöctane solution.

(1) M. Levy and M. Szwarc, THIS JOURNAL, **77**, 1949 (1955).

(2) M. Szwarc, *J. Polymer Sci.*, **16**, 367 (1955).

(3) F. Leavitt, M. Levy, M. Szwarc and V. Stannett, THIS JOURNAL, **77**, 5493 (1955).